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NEUROLOGIC CHANGES IN THE AGED

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THERE is something artificial about restricting to the central nervous system a discussion of aging. The only excuse is that, in a symposium such as this, it is convenient to parcellate the subject matter. A neurologist is in a particularly strong position to contribute toward the total problem, in that his speciality can be said also to embrace the psychologic and psychiatric attitudes, and to include a histologic study of the highly sensitive and fundamental organ of personality, mentation, and behavior: in other words, the physical counterpart of the organism.

Much of what a neurologist can contribute is purely factual and entails a mere descriptive approach. He supplies the bricks and mortar which may eventually be incorporated within the edifice of our understanding of the nature of aging processes in general. But description is not enough. It is a relatively simple matter to make precise observations, be they psychometric, clinical, histologic or clinical, upon the complex problem of the neurology of old age. To comprehend these findings, however, and to apply them, are matters which are much more difficult to accomplish, and yet at the same time they are far more valuable. I shall therefore first merely record the simple facts about the senile nervous system. Second, I shall try to indicate in more speculative fashion where the data may perhaps assist our approach to an eventual threefold goal—namely, an understanding of the nature of the processes of aging: the securing of mental and physical efficiency throughout the senium, and the extension of the life span.

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Unfortunately, the aging of the nervous system cannot be regarded as a "clean" or "tidy" experiment on the part of nature. The subject matter is much too overlaid with epiphenomena and coincidentals. Among the many inherent difficulties of the research we can enumerate two: in the first place, side by side with the aging of the central nervous system properly speaking, degenerative alterations are also taking place in the cerebrospinal vasculature. These changes of themselves are likely to produce additional manifestations. To separate the pathologic and clinical evidences of primary involution from those of focal or general anoxia is no easy matter.

Second, in the aging of the nervous system (quite apart from its vasculature), we are doubtless observing a dual phenomenon, partly physiologic and partly pathologic. The former includes the pure uncomplicated evidences of simple involution, the final stages of a lifelong biologic process of development, maturity, and decline. Such changes are natural, inevitable, and irreversible. This side of the problem may be spoken of as constituting the primary aspect of aging. The secondary or pathologic aspects comprise the *senium ex morbo*, made up of the accumulated sequelae, which remains like scars, bearing witness to the strains, stresses and wear and tear of a long life, together with the ravages of ill-health, self-indulgence, disease, injury, and malnutrition, which have been going on ever since birth. This aspect of the problem is additional, accidental—avoidable perhaps—and even reversible to some extent.

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These two classes of pathologic phenomena are sometimes also correlated with the origins of the aging processes and are thus spoken of as the primary and secondary *causes* of the aging of the nervous system. Or, they may be called endogenous as opposed to exogenous causes of decay. In this way it seems possible to reconcile the adherents of the two rival schools of thought, who have hitherto not been able to agree as to the essential nature of senescence. On the one hand, there were those who held the view that aging is biologic and natural (Marinesco,[1] Warthin.[2]) The opponents regard old age as a disease in itself (Cicero,[3] Allbutt,[4] Metchnikoff,[5] Tilney.[6]) A compromise must surely be struck between those extremists in either camp. Let no one assert that the discussion is a mere scholastic quibble, one which need not be taken seriously. The fundamentals of gerontology turn upon a scrutiny of this important difference of opinion.*

In so far as a study of the neurology of old age promises to illuminate our knowledge of aging processes, we may assert that psychology and psychiatry probably offer rather better prospects for research than a simple semeiologic approach. Thus the vexed question of relationship between the mental life of the normal senescent, and that of the senile dement, is one which still provokes

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***How to define the process of aging is a question which not unnaturally arises here. Many attempts have been made, some of them philosophic, others biologic. Clark's definition of old age[7] as "the period at which a man ceases to adjust himself to his environment" does not apply to healthy senescence: nor is it sufficiently dynamic to be satisfactory. Minot's suggestion[8] is preferable in that respect. He looked upon the rate of growth as the best method of measuring vitality, for it diminishes steadily throughout life and finally ceases. "Life is growth, the retardation of growth is old age, and its cessation is death." Lansing[9] has put forward a definition of aging as "a process of unfavourable progressive change, usually correlated with the passage of time; becoming apparent after maturity, and terminating invariably in the death of the individual."**

discussion (Létienne,[10] Lhermitte and Nicolas,[11] Krapf,[12] Roth,[13] Humboldt, Medawar,[14] Sjögren.[15]) But this important topic is the responsibility of other speakers. My task, however artificial in its restriction, will be to examine the clinical neurologic phenomena associated with extreme old age, excluding considerations which are purely psychologic. The scope of my communication is limited to clinical matters, and the interesting subject of the pathology of the aging nervous system will not be undertaken.

The neurologic changes in the aged will be discussed under two headings. First of all the neurologic signs of "normal" aged individuals will be described. Second, certain neurologic disorders will be dealt with, which are often regarded as being specifically senile in character.

THE NEUROLOGIC SIGNS OF "NORMAL" AGED PERSONS

Every experienced clinical neurologist realizes that the ordinary standards of diagnosis do not apply to the very aged, that is, those lingering on into the tenth and eleventh decades of life. In other words, the hallmarks of the "normal" nervous system are not necessarily valid within the senium.

Unless we constantly bear in mind the fact that our standards of normalcy are different in the aged from those in adulthood, we run the risk of diagnosing neurologic disorders where none actually exists. It needs to be stressed, therefore, that with advancing years certain changes occur so often as to be discounted as evidence of disease (Critchley,[16a, b] Howell[17]). Chief among the deviations are the following:

1. *Pupillary Changes.*—These comprise a tendency toward miosis together with a sluggishness in reflex response to light and also on accommodation. A stage may be reached, and later surmounted, when the pupils are inactive to light though still contracting on accommodation. These clinical changes are the result of alterations within the musculature of the sphincter pupillae, including fibrosis, hyalinization, and lipoid infiltration.

2. *Ocular Movements.*—With advancing years there is a progressive restriction in the movement of convergence. Defective conjugate upward gaze is also a common "normal" finding in the elderly.

> Special mention may be made here of the familiar ocular evidence of aging, namely, the presence of an arcus senilis or gerontoxon. This represents merely the most conspicuous manifestation of a much more widely spread lipoid infiltration of the tissues, including the iris, ciliary body, the sclera, and the membranes of Bowman, Descemet, and of Bruch. The earliest sign is a crescentic strip of cloudiness in the lower sector of the cornea; later, a similar arc appears in the upper part ordinarily covered by the eyelid. Later still these arcs fuse to form a ring-like structure separated from the rim of the cornea by the narrow "lucid interval" of Vogt. The relationship of the arcus senilis to chronologic age is not straightforward; nor indeed is the correlation with arterial degeneration very close. There may perhaps be a closer correlation between arcus senilis and hypercholesterinemia, for a similar condition has been produced experimentally in rabbits by overfeeding with cholestrol. Further clinical studies of the incidence of the arcus senilis are needed with special reference to its distribution within the aged population.

3. *Muscular Wasting.*—This condition is commonly found in advanced old age, as a thinly spread generalized amyotrophy. The histologic counterpart is a shrinkage both in the number of muscle fibers and in their individual bulk. Often this muscular wasting is particularly conspicuous in certain regions, as, for example, in the small muscles of the hand. Should there be concomitant deformities in the joints of the wrists and fingers, an arthritic muscular atrophy is often demonstrable over and above the senile amyotrophy. Fibrillation and fasciculation do not usually appear in cases of senile muscular atrophy, except in certain morbid conditions which will be considered later.

4. *Tremor.*—Tremor is popularly regarded as a common and indeed "normal" manifestation of old age. It is probably specified as one of the evidences of aging in the classical description to be found in Ecclesiastes (XII: 3), where we read ". . . the keepers of the house [i.e., the hands] shall tremble."

5. Although close and accurate testing of common sensibility is often a matter of extreme difficulty in the aged, it is quite easy to determine that the threshold for light touch and more especially for pain is definitely raised. Even better known is the fact that the appreciation of a vibrating tuning fork tends to lessen with advancing years (Kekcheev and Belova,[18] Laidlaw and Hamilton,[19] Pearson,[20] Critchley,[16a,b] Birren,[21]). Blunting of vibratory sensibility is commonly ascribed to defective vascularity of the white matter of the spinal cord. This hypothesis does not explain the factor of selectivity, i.e., why the function of certain long tracts such as the lateral columns should be unaffected, while some of the ascending pathways are involved. While upon this topic we recall the pathologic changes found by Fluegel,[22] in the spinal cord of a series of six persons over 80 years of age, despite ". . . une integrité fonctionelle presque complète." Unfortunately the author did not specify the precise neurologic findings in his patients.

Within the domain of the special senses a similar dulling of the acuity of perception may be found, leading to presbyopia, presbyacusis, and presbyageusia. These objective findings within the afferent nervous system tally with the ordinary clinical experience that, in the aged, many general diseases and also injuries seem to be attended by less pain than might be expected.

6. Many of the reflex phenomena used in routine testing behave differently in the case of the aged subject. Thus the tendon jerks may prove difficult to elicit. This is particularly so in the case of the ankle jerks, which are not infrequently quite unobtainable. The knee jerks usually persist, however. Arm reflexes (supinator, biceps, and triceps jerks) occupy a position midway between the behavior of the knee and the ankle jerks.

Loss of ankle jerks in old people may be the consequence of inelasticity of the tendo achillis rather than necessarily of changes within the reflex arc at a spinal level.

Increasing difficulty in the elicitation of the abdominal responses is well known; they may indeed be unobtainable as early in life as middle age. This is true largely because of the frequency with which the musculature has been overstretched, either by childbearing or by adiposity.

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The plantar responses are often very difficult to interpret in the aged. While a frank extensor response must be regarded as an exceptional finding, it is equally true that a clear-cut flexor response is but rarely seen. Various factors combine to complicate the test. Deformities of the feet, with valgus or equinovalgus resting attitudes of the great toe; stiffness or ankylosis of the first metatarsophalangeal joint; hardening of the skin of the sole with relative insensitivity—these are some of the common conditions which make it difficult for the clinician to elicit a response or to interpret whatever movement should occur.

It would be unwise to conclude that the foregoing reflex phenomena necessarily indicate an underlying structural senile alteration within the nervous system. Involutional changes in the muscles, tendons, ligaments, and periarticular tissues probably play an important part in making these superficial and tendon reflexes sluggish or unobtainable.

In contemplating the clinical effects of aging of the nervous system, we arrive at some interesting and perhaps unexpected ideas. The involutional process is a diffuse one affecting all levels of the neuraxis simultaneously. It is tempting to regard the resulting picture as a clinical expression of a gradual dissolution of the nervous system, in the Jacksonian sense. Such a dissolution might be expected more or less to recapitulate in reverse some of the evolutionary stages. Older mechanisms should prove more resistant to change, younger structures and functions being more vulnerable.

Clinical experience does not altogether bear out this anticipation. A neurologist, studying the aging of the nervous system from a structural standpoint—leaving aside purely mental functions—might well comment upon the relative infrequency of signs of cerebellar defect and also of pyramidal impairment. But, on the other hand, certain extrapyramidal manifestations are very common. If one can make a distinction here between hyperkinetic and akinetic extrapyramidal signs, we can emphasize that it is the latter type of change which we witness in old age. Tremor apart, such spontaneous movements as dystonia, athetosis, chorea, are rare; indeed they hold no place within the neurologic picture of normal old age.

Common in the aged, however, are the so-called akinetic-hypertonic signs, which in their fullest development constitute a Parkinsonian-like "amyostatic" syndrome, without tremor (Critchley,[16a,b,23]). Minor extrapyramidal signs are so commonly present in the aged that they are apt to be overlooked, or rather to be put down to a general loss of the elasticity of the tissue. But most of those numerous little signs and manifestations, the characteristic gestures, the attitude, stance, and gait of the elderly—distinguishing them so sharply from the youthful—are really features of an extrapyramidal order. Thus the young actor, in assuming the role of an old man, actually adopts and unwittingly asssumes many components of an extrapyramidal syndrome.

An attitude of general flexion is also one of the hallmarks of old age. Head and neck are held craned forward; there is a gentle dorsal kyphosis; upper limbs are bent at elbows and wrists; while the hips and knees are also slightly flexed. Here again we may quote the twelfth chapter of Ecclesiastes, where we find ". . . the strong men [i.e., the legs] shall bow themselves." In marked cases, the

degree of flexion may be extreme, and mimic advanced Parkinson's disease. When the old person lies supine, his neck may remain bent so that the occiput is off the pillow. Abnormal attitudes of the hands are very common, and indeed the appearance of the hands is only too often a revealing indication of the age of the individual. Here as elsewhere, joint deformities may exaggerate the involutional picture.

We are probably justified in attributing the flexed attitude of old age, in part at least, to extrapyramidal factors. But we must certainly not overlook the role played by other associated changes in the vertebral column and in the intervertebral discs: ankylosing disorders of the ligaments and joints, shrinkage and sclerosis of the tendons and muscles, all contribute to the total picture. Indeed we must not forget that some extreme cases of arthritis deformans and of spondylose rhizomélique superficially resemble a Parkinsonian syndrome and may sometimes occasion diagnostic confusion. Muscular rigidity is another common finding in the aged, especially when considerable cerebrovascular degeneration is also present. Foerster spoke of this condition as an arteriosclerotic rigidity. It is demonstrable clinically by a uniform resistance to passive manipulations, especially in the limbs and in the neck. Proximal segments of an extremity are more affected than the distal: legs more than arms. At the bedside it becomes obvious that the phenomenon of rigidity is no simple matter. There is even a "mental" component in many cases, especially when arteriopathy coexists. Thus the rigidity may vary directly with the amount of force used by the examiner in passive manipulation. Again, if the patient's attention is distracted from the maneuvering of the limbs, the rigidity becomes less. This fact often leads to the assumption that the subject is "not relaxing." But it would be wrong to dismiss this finding as a mere accidental complicating factor—the evidence of wilful noncooperation on the part of the aged patient. To some extent it is attributable to a lack of comprehension of the examiner's wishes; in such cases passive movement of limbs may produce an automatic and almost "reflex" tightening of the muscles, as if in opposition. In somewhat exaggerated form, this constitutes a "psychomotor negativism," in the words of Kleist.[24] Still more striking is Kleist's phenomenon of "counterpull" (*Gegenhalten*) where a tonic contraction is brought about by passive movement.

Mental influences which affect the motility of the aged may also be traced in a tendency toward motor perseveration—itself an expression of ideational inertia. To some extent, senile or arteriosclerotic rigidity may be looked upon as an index of perseveration, whereby rapidly alternating passive movements tend to be resisted. This mental influence is shown by two phenomena. In the first place, after a limb has been passively flexed and extended several times and then abruptly released, the patient may continue to make feeble flexion-extension movements, thus actively simulating the passive movements carried out by the examiner. These palipraxic aftermovements continue for only a short time. The second illustration of a mental influence consists in the assumption of catatonic postures. The aged person may allow his limb to be retained in whatever position it is placed, even in defiance of gravity. Such a phenomenon results from a combination of extrapyramidal factors with some degree of

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dementia. This is probably what Steck[25] had in mind when he spoke of catatonia as being a link connecting organic with functional phenomena. As I have written elsewhere,[23] defective mentation is an important influence in determining catatonia in cases of senile (or arteriosclerotic) rigidity. Inadequate perception, lack of attention, and retarded cerebration combine to produce an ideational inertia, or mental viscosity. The subject fails to grasp successive concepts if they should follow too closely one after another. If the suggestion takes the form of an attitude passively imposed upon a limb, the posture tends to be maintained for an inordinate length of time. Two explanations are possible. Either the subject is temporarily oblivious of the existence of the limb, the proprioceptive impulses failing to attain awareness; or, on the other hand, the subject's sensorium may be replete with the idea of the attitude which has been passively ordained, to the exclusion of fresh ideas. Not until the initial suggestion wanes, or is replaced by awareness of the painful impulses from the tiring muscles, is the catatonic attitude interrupted.

Another motor sign characteristic of extrapyramidal disorder is to be found in a general poverty of movement. Although the aged person is not paralyzed in any sense of the word, he seems to make as few movements as possible. He does not exert himself, but behaves as though the effort to move were too great. This relative immobility shows itself in the impassive facial expression; the infrequent blinking of the eyelids; and the statuesque attitude so typical of those advanced in years. When he wishes to look far over to one side or the other, the elderly person moves his eyes first. Then the head, neck, and shoulders slowly follow, and all in a piece. The quick nervous gestures, the birdlike movements of so many vivacious young persons, the movements of rhetoric, expression, and emotional display are not seen in the aged. In their stead a certain poise or calmness is found. Old people sit for long periods without changing their position, crossing and uncrossing their legs, folding their arms, fidgeting with their hands, or gazing around.

At the same time it must be emphasized that the so-called "associated movements" (which may be said to include all secondary movements, synergias and movements of cooperation) are not actually in abeyance, but are merely reduced in amplitude and speed.

Finally, the extrapyramidal-like picture is completed by a characteristic slowness of movement. We may not perhaps altogether understand what it is that determines the rate of a particular movement—willed, voluntary, volitional, automatic, instinctive—in a normal young adult. Unquestionably, however, this rate is reduced in the aged, just as it is in victims of Parkinson's disease. Slowness also involves actions which can be roughly termed "automatic" rather than highly volitional. Thus the passage of the fork to the mouth at mealtime; the champing of the jaws; the flicking away of a fly from setting upon the brow; all these actions are just as retarded as those which are deliberately executed in response to a command.

The foregoing components of extrapyramidal impairment—namely, a flexion attitude, rigidity, infrequency and slowness of movement—constitute, when intense, a sort of Parkinsonian state. But in minor degree they are so commonly

met with in normal old people as to establish a hallmark of the aging nervous system. It might therefore be argued that the extrapyramidal system, though commonly regarded as the "old" motor system, is apparently more vulnerable to aging processes than some of the "younger" corticifugal efferent pathways. Or perhaps the matter could be better expressed in somewhat different terms. Can it be that the clinical expression of a diffuse, thinly spread neuropathologic process is to be seen in an extrapyramidal picture rather than, say, a pyramidal, or hyperkinetic, or cerebellar, or sensory syndrome? Extrapyramidal sings, in other words, may comprise a sort of clinical "least common multiple" of neuronic dissolution.

NEUROLOGIC DISORDERS PECULIAR TO THE SENIUM

The recognition of neurologic disease in the aged is complicated by one or two inherent difficulties. Thus a chronic malady may begin in youth or middle life and extend into the senium by dint of its irreversible character. A consideration of such disorders is not called for here. Second, a particular malady may happen by chance to make its first appearance in extreme old age. This topic of delayed development of disease, although not without its own specific problems of interest, is not strictly relevant. A third complicating factor is more difficult. The nervous system of a very old person may be involved secondarily: that is to say, as the result of primary senile disease of extraneural tissues. For example, neurologic syndromes may complicate a spondylosis or disc degeneration. Still more difficult to extricate are the neurologic disorders which are consequent upon primary disease of the cerbrospinal arterial system. Last, there remain the senile disorders of the nervous system which can be regarded as "pure" or specific. In ordinary practice the two last groups of cases occur so intimately linked that to try and disentangle them becomes a rather artificial task.

It is interesting to recall the records of 16,000 patients compiled by Lewellys Barker.[26] Out of this series, there were 300 patients who applied for consultation over a period of seven years. Of this total, 240 cases were in the seventh decade of life, 57 were in the eighth, and 3 were in the ninth. The subjective complaints of the 240 patients aged between 60 and 70 years were analyzed, and it was found that by far the commonest symptoms were referable to the nervous system. These comprised (1) depression (29 cases); (2) nervousness (26 cases); (3) fatigability (23 cases); (4) insomnia (20 cases); (5) anxiety (13 cases); (6) acroparesthesias (11 cases); (7) headaches, and other cephalic sensations (10 cases); (8) dizziness (9 cases); (9) visual disturbances (9 cases); (10) tremor (8 cases); (11) failing memory (5 cases); (12) "fainting spells" (5) cases; (13) deafness (5 cases); (14) disorders of speech (3 cases); (15) tinnitus (3 cases); (16) difficulty in walking (2 cases); and (17) "sciatica" in two cases. When the final diagnoses were analyzed it was found that nervous maladies took second place to circulatory affections. The neurologic diagnoses included psychogenic disorders (43 instances); Parkinson's disease (7 instances); senile psychoses (4 cases); paralysis secondary to organic brain disease (3 cases); and "organic encephalopathy of doubtful nature" (3 cases).

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Lewellys Barker's figures may be compared with one's own case records taken from a consulting neurologic (and nonpsychiatric) practice. In the nine-year period, 1946-1955, 252 new patients of 70 years of age and over were seen in private practice. (Hospital patients are not included.) The diagnoses arrived at in these cases may be set out in tabular form (Table I).

TABLE I

DIAGNOSIS		NUMBER OF CASES
Cerebrovascular Degeneration including hypertension, senile epilepsy, temporal arteritis, and peripheral vascular disease		107
Neurotic and Psychotic Problems including dementia, depression, hypochondria, confusional states and anxiety (all exclusive of arteriopathy)		29
Parkinson's Disease (excluding arteriosclerotic Parkinsonism)		23
Neuralgia		
trigeminal	10	
postherpetic	15	
other types	4	29
Headaches		
? cause		11
Backache		4
Spondylosis and spondylitis		6
Carcinomatosis with neurologic involvement		5
Cerebellar Atrophy		5
Progressive Spastic Bulbar Palsy (excluding "pseudobulbar palsy")		3
Combined Degeneration of the Spinal Cord		3
"Senile Paraplegia"		8
Acroparesthesia including the carpal tunnel syndrome		2
Sequelae of Head Injury including subdural hematoma		7
Peripheral Neuropathy		
diabetic	1	
carcinomatous (included above)	1	
"sciatica"	3	4
Cerebral Tumor (excluding metastatic carcinoma of the brain)		3
Senile (essential) Tremor		1
Vertigo		1
Narcolepsy		1
Total		252

The genuine specific neurologic disorders of the senium are few in number, and rare in occurrence. Two or three clinical syndromes deserve attention, particularly senile tremor, senile paraplegia, the senile muscular atrophies, senile epilepsy, and giant-cell arteritis.

Senile Tremor.—Tremor has been regarded for centuries as a normal and integral appanage of senility. It is strange that this idea has persisted despite the evidence afforded by neurologists that tremor in old age is actually an uncommon feature. Thus, as long ago as 1876 Charcot[27] registered a protest, and he estimated that out of an aged population of about two thousand inmates of the Hospice de la Salpêtrière, instances of tremor numbered no more than thirty.

Nowadays it is realized that senile tremor is merely a particular example of "essential" or "idiopathic" tremor, happening to appear first in extreme age (Critchley[28]). Although this was the teaching laid down by Trousseau in 1885,[29] it did not gain acceptance until quite recently. That essential tremor is also familial tremor is yet another conception which developed slowly, even though it had been affirmed by Most[30] in 1836. When adequate pedigrees are available for scrutiny, it becomes obvious that "anticipation" is an important genetic property of these cases of tremor. Thus, characteristically, senile tremor which appeared in the first affected generation crops up earlier and earlier in successive generations, and appears as a presenile, an adult, a juvenile, an infantile, and, finally, a congenital variety of tremor.

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Though the morbid anatomy of senile (essential) tremor is unknown, the clinical features are familiar. The tremor may affect the head, jaw, and hands, or any combination of these regions. In the head there may be a fine, nodding tremor ("tremblement affirmatif"); or a side-to-side movement ("tremblement negatif"). Tremor of the mandible shows itself as a persistent champing or chewing. Sometimes there is a repetitive movement of the lower part of the face, especially of the lips and of the mentalis muscle (cf. Démange's patient,[31] dubbed "old rabbit face", 1882). In the hands the tremor may be slow and coarse (four per second), or finer and more rapid (twelve per second). The former type is reminiscent of the Parkinsonian tremor, while the latter resembles the tremulousness of hyperthyroidal states. The tremor may be temporarily inhibited by willed movements of the limbs. Or it may become exaggerated. In the latter case the resemblances to a cerebellar type of tremor are very close. Senile tremor is increased by fatigue, by cold, and by emotional stress. Often it is temporarily relieved by taking alcohol. Senile tremor may interfere with the performance of delicate finger movements and it characteristically distorts the handwriting. Progressive attenuation of the script does not occur, however, and hence there is no real resemblance to the micrographia of the Parkinsonian.

Essential tremor is ordinarily not associated with rigidity, poverty, or slowness of movements, and these are important criteria in excluding Parkinson's disease. But in extreme old age some degree of rigidity, hypokinesis and bradykinesis may happen to occur as part of the simple picture of old age. Consequently, it is more difficult to differentiate paralysis agitans from senile tremor, than from essential tremor in a younger subject.

No discussion of senile (essential) tremor can omit reference to the interesting assertion that Minor,[32-36] Katzenstein,[37] and others have made concerning the families of affected members. Many authors have drawn attention to the presence of longevity and fecundity in the family trees, a phenomenon which Minor termed the *status macrobioticus multiparus*. Others have elaborated this idea and have claimed that patients with senile (essential) tremor are highly intelligent, virile personalities who both work hard and play hard, eat heavily, drink deeply, and are sexually lusty. Quite aside from this notion of *macrobiosis*, there is evidence that in some families senile (essential) tremor constitutes a *forme fruste* of some other and better defined neurologic disorder. Two diseases have been specifically mentioned in this connection, namely, presenile cerebellar atrophy and Parkinson's disease. As regards the latter we recall that no sharp nosologic demarcation was believed to exist between Parkinson's disease and senile tremor by such authorities as Gowers,[38] Pelnár,[39] Gelma,[40] and Noïca.[41] An association between senile tremor and senile cerebellar atrophy has been mooted by Schuster[42] and by Critchley and Greenfield.[43]

Senile Disorders of Gait.—This term is deliberately chosen in preference to "senile paraplegia," for neither pathogenesis nor morbid anatomy is uniform. "Paraplegia" is also a misnomer at times, for the clinical disability is more in the nature of a "dysbasia" or a mere difficulty in walking; and actual paralysis—as tested upon a supine patient—may not be demonstrable. More satisfactory terms therefore would be "senile disorders of gait," or "dysbasia occurring in old age" (Critchley[44]).

Earlier neurologists wrote as though there existed a clear-cut clinical entity characterized by paralysis of the lower limbs in old people and it is to Gowers[45] that we probably owe the term "senile paraplegia." It was first used in print by Kelly.[46] Later experience has shown that the problem is far more complicated; that weakness of the legs in old people can result from lesions at various levels in the nervous system, and furthermore that even nonneurologic alterations can produce difficulty in standing and walking. The monograph of Lhermitte[47] enumerated the causes of paraplegia in the aged as "cerebral," "spinal," and "muscular." Nowadays it is usual to include various subcortical pathologies among the causes of disordered gait in the senium.

Cortical paraplegia may occasionally occur in the aged as the result of an abrupt and solitary vascular accident. This comes about when the anterior cerebral artery of one side happens to supply both cerebral hemispheres, by way of an unusually large anterior communicating artery. This anatomic anomaly is by no means rare. In such cases an occlusion of the main trunk of the hypertrophied anterior cerebral artery will produce softening within both paracentral lobules. Clinically this will result in a sudden weakness of the distal segments of both legs—a bilateral syndrome of the anterior cerebral artery.

In geriatric experience it is again not rare to find a bilateral weakness developing after an isolated apoplectic hemiplegia. An aged person sustains a stroke which produces a one-sided paralysis. He takes to his bed. As weeks go by, and in the absence of nursing and remedial care, the opposite nonparalyzed leg

becomes more and more stiff, contracted, and feeble. Eventually a state of affairs is reached whereby both legs lie in an attitude of flexion—the paralyzed limb being everted and externally rotated, while the leg on the sound side is inverted and internally rotated. Both knees are firmly pressed together and passive correction of the deformities is impossible.

There exists a large and miscellaneous group of cases where the aged person's ability to walk is considerably impaired, though the legs are not, strictly speaking, paralyzed. When the patient's motor power is tested as he lies in bed, no great disability can be found. But the patient cannot walk unsupported. He may be most unwilling to make any attempt to do so. Encouraged, however, he hesitatingly and fearfully advances in short, shuffling steps, frantically clutching the furniture or the bystanders. After a step or two, the legs may give way; or the patient may stagger wildly; or one leg may cross in front of the other. This is the "astasie trépidante" of the French neurologists; a variant is sometimes spoken of as Petrén's gait.[48] Here the patient makes a few tiny steps and then comes to a standstill; with coaxing, however, he steps out almost normally. Again after a few paces he halts and is reluctant to proceed. With further encouragement, however, he starts again. So it continues: a few steps, and then a pause, and so on again.

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There has been some discussion as to the nature of this type of gait disorder (von Malaisé[49]). Some have looked upon the trouble as evidence of a senile hysteria. Others have regarded the disability as being apraxic in nature (Vogt and Maas,[50] Sittig[51]). Quesnel[52] discussed functional disorders of gait as occurring in the aged and recognized three clinical groups: (a) a mild and readily curable disability; (b) more severe impairment, associated with mental disease; and (c) an organofunctional type in which structural disease of the bones, joints, or nerves may be present. In this third group belong those cases of functional paraplegia supervening in patients bedridden because of a fracture.

It is also common to see in aged subjects the characteristic difficulties in walking which are so typical of the arteriopath. Here belong the small-steppage gait of the patient with progressive lacunar disintegration, with pseudobulbar palsy, or with arteriosclerotic Parkinsonism. Sometimes the gait is so disordered as to be ridiculous. The patient shuffles along, swinging his arms in an exaggerated fashion, advancing the toes only an inch or so with every step. The feet are rapidly slid along the ground, not lifted. When the patient attempts to turn, his tiny paces become exaggerated in rate, though reduced in amplitude, in a fantastic fashion.

Senile disorders of gait from spinal lesions are probably rarer. This statement holds particularly true if we except from this category what must surely constitute the most common cause, namely, partial spinal compression from cervical spondylosis. Vertebral lesions apart, spinal paraparesis in the aged may perhaps also occur as a result of a senile combined sclerosis within the spinal cords of aged persons. Perhaps that is to carry an attempt at pathologic precision too far.

The muscles and tendons of the legs may themselves be the seat of advanced fibrotic changes to such a degree as to interfere with functional activity. The

central and peripheral nervous systems are not necessarily involved. This is the condition originally described by Lhermitte under the term "senile myopathy" or "myosclerosis," and which resembles in many ways the clinical picture of dermatomyositis in younger subjects Lejonne and Lhermitte,[53] Fumet,[54] Lhermitte.[55] Aged patients rendered bedfast by reason of some incapacity—cardiac or pulmonary perhaps—often slowly develop this myosclerotic contracture of their lower limbs. The muscles become hard to the touch and somewhat tender, and the overlying skin is bound down to the deeper tissues. The muscle bellies and the tendons stand out conspicuously. A flexion attitude of the legs gradually develops and eventually becomes extreme. Passive correction of the new posture is impossible even under deep anesthesia and active movements are considerably restricted. Standing and walking are quite beyond the patient's capacity.

This condition of progressive myosclerosis of the lower limbs is not at all rare and may be only too often witnessed in institutions for the aged or in domiciliary patients. Immobility is the most important etiological factor, and this may be the consequence of neglect or inadequate nursing care. Despite its common occurrence, this syndrome has received scant attention in the neurologic literature.

Senile Muscular Atrophy.—Within this category belongs a number of ill-defined conditions where localized muscular wasting shows up prominently against a background of a more evenly spread atrophy. Involuntary movements may be visible which can be variously described as "fibrillation" or "fasciculation." Usually the condition is intermediate between these two, and the flickering shows itself particularly when the affected muscles are in active contraction, as during the performance of a voluntary movement. Cramps are also a frequent complaint referred to the affected musculature, and they may occur during states of rest (as in bed at night) or during activity.

One characteristic variety of localized muscular wasting in the aged is to be found in the hand. Most very old persons have a certain thinning of the small manual muscles, which imparts a somewhat clawlike appearance. Should an arthritis of the wrist or of the knuckles also be present, the muscle wasting is intensified. But the clinical picture of a senile myatrophy of the hand is even more striking when fibrillation also occurs, and when there are no gross changes in the metacarpophalangeal joints. Sometimes the atrophy is limited to the muscles of the thumb, as in the "anterior tephromalacia" of Marie and Foix.[56] Lhermitte and his associates (Lhermitte and Nicolas,[57] Lhermitte and de Massary[58]), have devoted much attention to this condition and to its possible pathogenesis. They have raised the interesting suggestion that the group of nerve cells in the ventral cornua of the sixth and seventh cervical segments, corresponding with the innervation of the thumb, is in a precarious state as regards its arterial supply, so that a senile endarteritis would easily lead to a local ischemia of that part of the spinal gray matter.

A more diffuse state of spreading muscular atrophy may also occur in the aged. Cramps and flickering within the muscles may constitute the chief subjective complaints. In some ways the clinical picture resembles that of motor neuron disease, and especially the Aran-Duchenne variety. On the other hand,

it does not inexorably advance and lead to death from bulbar involvement. More commonly it worsens only up to a point, and, thereafter, it seems to halt, neither progressing nor regressing. Cases of this type were described long ago by Oppenheim; and by Michell Clarke[59]; and recently by Neumayer.[60]

Senile Chorea.—Chorea deserves mention among the specific neurologic affections of the senium. Admittedly it is a great rarity, for one must be careful to exclude the possibility of a Huntington's chorea of unusually late development. Indeed we must at all times consider the possibility of there being a remote connection between Huntington's disease and senile chorea, and we recall Haldane's suggestion that, as the centuries go by, Huntington's chorea may be changing its natural properties by tending to show its first signs at a progressively later age.

Sufficient pathologic evidence exists to support the demarcation of a rare disorder of the senium characterized clinically by the late and gradual appearance of choreiform movements without any genetic properties, and without any demential changes other than mild intellectual enfeeblement consistent with the patient's age. Such cases are attended on the pathologic side by neuronic outfall in the putamen and candatum without any gross ischemic lesions, and without any affection of the corpus Luysii or of the cortex (Alcock[61]).

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Among the specific disorders of the senium, we may also refer to one which embraces both neurologic and psychiatric features, namely Jakob's disease. This term is one which might be appropriately applied to the condition originally termed "senile Vorsteifung" or "senile Muskelstarre" (Jakob[62]). A condition of marked dementia, occurring in the aged, is associated clinically with severe extrapyramidal disorder. The neurologic picture is rather like that of a Parkinson's disease *sine tremore*, occurring in an unusually aged subject. From a pathologic standpoint there occurs nerve-cell atrophy in the cortex and in the basal ganglia, especially the pallidum. Senile plaques are demonstrable within the globus pallidus.

Senile Epilepsy.—This term includes a variety of disorders of consciousness which may first show themselves in the elderly. Convulsive manifestations are not always present and the term "senile syncope" might be preferable at times. Patients differ according to the depth and duration of the disturbed consciousness, the circumstances under which an attack occurs, and the consequent subjective state. Temporary excitement and confusion may follow each episode as in the variety of senile seizure specifically described by Barber.[63] A broad distinction may be made between the cases which are of "cardiac" origin and those which are "cerebral" in type. In both categories it may be said that degenerative vascular disease plays a role of great significance. A rarer clinical type of attack occupies a particular niche. This is the so-called "drop seizure," where the victim falls heavily to the ground without experiencing any promonitory dizziness or warning of any other kind. The patient usually denies having lost consciousness, but it is possible that an extremely brief interruption in the stream of consciousness may have occurred without his knowing it.

Giant-Cell Arteritis.—This may well be included among the specific disorders of the senium which may present themselves as neurologic problems.

Headache is not a particularly common complaint in the elderly so that the appearance, late in life, of very intense neuralgia-like pains localized within one area of the scalp, should lead to the suspicion of a temporal form of giant-cell arteritis. The adjective "temporal" is unfortunate, for the arterial disease is often very widespread; and even when it affects the head it is not necessarily a temporal artery which is most involved.[64] The diagnosis is not difficult, being assisted by a conspicuous distention of the affected artery, with exquisite tenderness upon handling. Concomitant visual symptoms, due to involvement of the retinal arteries, are common. There is generally a constitutional reaction, with low fever, malaise, loss in weight, eosinophilia, and a raised blood sedimentation rate.

The foregoing constitute the main specific neurologic affections of the senium. It would be wrong not to refer, however, to the notion of a possible limited and also premature type of aging within the nervous system. There immediately come to mind such conditions as the progressive cerebellar degenerations (olivopontocerebellar atrophy; delayed cortical cerebellar atrophy); Pick's presenile dementia due to localized symmetrical cortical atrophy; Alzheimer's psychosis; paralysis agitans; motor neuron disease; and even some of the heredocerebellar ataxias. It is not yet possible to account adequately for the selective decay of certain systemic or regional neuronic groupings in such conditions, and naturally the hypothesis of a premature involution comes up for discussion. This was specifically considered by Gowers, who employed the term "abiotrophy" to apply to an inherent endowment of a limited viability to a particular part of the nervous system.* Although Gowers' ideas and also his term "abiotrophy" have come in for criticism, the notion cannot be carelessly brushed aside. Gowers was very much alive to the speculative nature of his hypothesis and to the dangers of attaching a label to something imprecise and even nebulous. We recall that the Vogts also later conceived of a "pathoclisis" to explain local tissue vulnerability.

A correlation between the morbid anatomy of aging of the nervous system and the pathology of the hereditary ataxias has particularly attracted attention;

*Gowers' doctrine is so often involved, and his original description so rarely quoted, that it is perhaps desirable to reproduce some of the sentences contained in his lecture of February 21, 1902.[65]

". . . many of these parts have their own vitality. Some of them may slowly die, while the life of all the rest goes on without impairment. They may die from many causes, some early, inevitably, from a grave defect of vital endurance; some much later, the failure being but slightly premature; and some at various times, apparently from various causes. When the failure is early it is often due to a defect in vitality, a defect which seems to be inherent, the tendency thereto inborn. We do not, indeed, apply the word 'death' to this slow decay of the elements; we speak of it as 'degeneration', but the process is, in many cases, perhaps in most, an essential failure of vitality, and I think it instructive to consider the degenerations in this aspect. But in doing so I am met by the difficulty, that we have no word by which to designate this conception—a degeneration or decay in consequence of a defect of vital endurance. I do not like new words—indeed I dislike them—but if we have a conception for which no name exists, which we need frequently to speak of, it is not wise, I think, to shrink from an attempt to give it a name. Here, the simplest mode of obtaining what we need is to insert the root of βιος after the negative particle in "atrophy"; this gives us "abiotrophy." But it is generally better, if you can, to appropriate what you need than to make it afresh, and we find the word βιοτροφος used in the sense of "vital nutrition." If we prefix the negative particle we have the same word 'abiotrophy'. If a more general term is desired, the adjective 'biotic' has been occasionally used in English in the sense of vital, and from this we may form 'abiotic' to designate that which depends on defective vitality. A corresponding substantive would be 'abiosis', and this also has some warrant. The word βιοσις was employed once or twice in old Greek, meaning 'mode of life.' It is given us by the physician, who is more widely known and esteemed, on account of the character and precision of his writings and the devotion of his life, than any other medical man who has lived—St. Luke. It is pleasant, I think, to take a word from him. So I give you a choice of words by which to designate this unnamed conception."

Subsequent neurologists seem, however, to have agreed in prefering Gowers' first suggestion.

and more so in recent years. Gowers' paper[65] on abiotrophy dates from 1902. Raymond[66] stressed the relationship between familial disorders and a premature localized senescence in 1908. A similarity in the neuronic changes which occur both in aging and in the ataxias has been the subject of comment by Marinesco,[67] Orton,[68] and others. In a recent symposium upon genetic disorders, Schut[69] has drawn attention to a senile type of change in the skin of ataxic patients. He believed that the facial expression matures early, and that some ataxic individuals appear older than their actual age. Most clinical neurologists, however, would hesitate to accept these views unreservedly.

The doctrine of abiotrophy is, however, showing signs of being whittled away by advances in neurochemistry. Thus the earlier views of Jelgersma[70] and Lewy[71] that Parkinson's disease can be looked upon as a pallidal involution, is losing ground.[72] Motor neuron disease is more and more under suspicion of being a toxic disorder of the spinal cord, rather than a primary degeneration.

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DISCUSSION

The foregoing account of the nervous system in the aged aims at bringing up to date our present knowledge of the subject, inadequate though our ideas may be. It would be unwise to close the discussion without indicating the purely neurologic considerations where more data are needed and where there is promise of expansion in our understanding of old age in general.

In the first place, we need far more information as to the morbid anatomy of the senile nervous system. Léri's monograph[73] on the senile brain and Sander's studies[74] on the senile spinal cord merely opened important chapters, which are still far from being closed. Though there have been many subsequent descriptive accounts of the pathology of the senile nervous system, most of the cases studied have been examples of senile dementia and not of healthy old age. In far too many cases, information as to the patient's mental and physical condition before death has been quite inadequate. We require much more knowledge about the changes in the nervous system which are compatible with "normal" old age—that is to say, subjects who have died at a great age from some nonneurologic affection and who during life were in no way demented or psychotic.

The problem of the senile plaque is still of great interest to the clinicopathologic investigator. Despite the considerable literature upon this subject, we remain uncertain as to the meaning of these deposits—the "black marks of old age" as they have been called. More information is needed as to the occurrence of these structures outside of the senium; their precise distribution within the nervous system; their correlation with chronologic age, and with intellectual deterioration.

Of great interest, however, is the belief that senile plaques may, in part at any rate, signify the operation of a histochemical anomaly. Divry[75] looked upon senile plaques as the expression of a disseminated hyaloamylosis affecting the cortex. The traditional pragmatic attitude is therefore to regard them as evidence of a reactionary change directed against a specific metabolic process of toxic nature (Critchley[76]). First there occurs an involutional alteration in the chemistry of the ground substance embracing the neuronic elements. In

this way lipoid (or possibly amyloid) substances are precipitated. A microglial reaction is provoked. This hypothesis is of great interest in that it invokes a toxic element, as opposed to a simple decay from loss of vitality. It tempts one to speculate that those disorders of the senium which are characterized histologically by a profusion of plaques, may be, to some extent at any rate, exogenous, reactive, or secondary manifestations of an aging process (a *senium ex morbo* rather than a *senium naturale*).

Special attention might also be paid to the involutional changes which can be found within the structures constituting the blood-brain barrier. Here the choroid plexus comes up for particular notice. It is a structure which is exquisitely sensitive to senile changes. A wide range of alteration occurs in the histologic appearance of the choroid plexus between youth and age, and it is possible that evidences of aging are detectable here comparatively early. It is tempting to equate such changes in the plexus as occur with advancing years, with a progressive inadequacy in its role as a filter or barrier.

Another histologic problem which still requires elucidation is one to which I drew attention twenty-four years ago.[16a] I refer to the differences in the nervous tissue reaction to a known noxa, according to age. It would be a relatively simple matter, and perhaps an illuminating one, to compare and contrast the minute histologic changes within the cerebrum in cases of general paresis occurring in children, adults, and the aged. Or the glial reaction around a tumor, or a region of cerebral laceration, might well be studied and documented with reference to the actual age of the patient concerned.

Yet another problem deserves detailed examination along both histologic and clinical lines. I refer to those rare but highly important cases of precocious senility met with in childhood. Although we are fairly well conversant with the skeletal, dental, dermatologic, and endocrine reactions of these cases, we are still completely ignorant of the neurologic and neuropsychiatric aspects. We do not know, for example, whether such neurohistologic characteristics as senile plaques, Alzheimer's neurofibrillary tangles, or the Bouman type of Purkinje-cell change occur in cases of senium praecox, progeria, or even premature senility. We know nothing of intercurrent neurologic disease in such cases, or indeed what constitute the clinical norms on routine testing of the nervous system. We know but little of the intellectual capacity of such patients, or of their personalities or emotional life.

Let it not be asserted that discussion of this sort is academic or impractical. On the contrary, it is hard to conceive of a biologic problem which promises to be more utilitarian in its scope. It is to neurohistology that we look for information as to the relative importance of endogenous versus exogenous factors in the natural processes of old age. As already emphasized, herein lies the crux of the problem of extension of the life span and the preservation of mental and physical efficiency in the aged.

Although I have already used this quotation elsewhere[a] may I finish by repeating the words of Professor Tilney, uttered in 1928 in New York: "Some day, people will awaken to the fact that they have been missing the greatest constructive opportunities. . . . . One liberally supported and effective

brain institute would prove an incomparably more profitable investment for civilization than the most powerful battle-fleet that ever sailed the seas. The political party which will have the foresight and humanity to introduce into its platform an article advocating and supporting the longer and better use of the human brain will offer a worthy issue to its electorate."

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HUMAN CEREBRAL BLOOD FLOW AND OXYGEN CONSUMPTION AS RELATED TO AGING

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THE circulatory nutrition of the brain is one of the fundamental components upon which are built the more subtle, more complex, and less accessible frameworks of function. Over the past decade, a number of investigators have elicited information on the over-all circulation and oxygen consumption of the human brain at various ages over practically the entire life span. It seems appropriate to review these data, to observe whatever consistency or correlations appear, and to begin to form hypotheses to be tested in future work.

Investigators have used the nitrous oxide technique,[1] which yields an average value of blood flow per minute for unit weight for the brain as a whole, from which are derived similar units of oxygen consumption and vascular resistance. These data, therefore, incorporate any errors to which the nitrous oxide technique is subject. In addition, two of the investigating groups, whose results seem consistently higher than those of the others,[2-4] employed a later modification[3] of this technique in which it has recently been suggested that some systematic error may arise.[5] Although a precise evaluation of that error depends upon dead space and timing factors which are not always available, an attempt at correction of such data can be made from a comparison of values obtained in the range from 20 to 30 years of age where the results of other groups have been quite consistent. A correction factor of 0.85 thus obtained has been applied to their data in Figs. 1 to 3. The precise value of this correction or, indeed, whether it is necessary at all is somewhat irrelevant to the present argument since the data in question show the same relative trend with age as do the others.

In an effort to restrict the relevance to the normal processes of maturation and aging, some pains have been taken to include all of the series where age rather than disease was the primary variable, with the result that numerous series on hypertension, arteriosclerosis, and the psychoses of the senium were excluded. Nevertheless, the series included represent only an approximation to the normal aging process, since practically all represent hospitalized patients, even though

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their diseases were unlikely to affect the cerebral circulation. The sources of these data, the mean age and number of cases in each series, are given in Table I.

TABLE I. DATA AND SOURCES

AUTHORS	NO. CASES	MEAN AGE	CBF*	$CMRO_2$†	CVR‡	$(A\text{-}V)O_2$§
Kennedy et al.[6]	6	5	104	5.1	0.8	4.8
Kennedy et al.[7]	7	10	90	5.3	0.9	6.2
Kennedy et al.[7]	7	13	68	4.0	1.4	6.0
Sokoloff et al.[8,9]	4	19	60	3.70	1.5	6.2
Sokoloff et al.[8,9]	7	23	52	3.12	1.8	6.3
Kety and Schmidt[1]	14	25	54	3.3	1.6	6.3
Scheinberg and Stead[3]	19	25	65‖	3.8‖	1.3‖	6.0
Schieve and Wilson[4]	12	29	62‖	4.0‖		6.6
Shenkin et al.[10]	12	30	53	3.4	1.8	6.6
Fazekas et al.[11]	9	34	54	3.5	2.1	6.5
Schieve and Wilson[4]	10	40	57‖	3.5‖		6.4
Scheinberg et al.[2]	16	50	59‖	3.8‖	1.6‖	6.4
Scheinberg et al.[2]	16	63	51‖	3.4‖	2.0‖	6.7
Schieve and Wilson[4]	7	64	55‖	3.7‖		6.7
Fazekas et al.[11]	15	68	43	2.4	2.9	5.5
Fazekas et al.[12]	18	93	39	2.3	2.7	5.8¶

*CBF represents cerebral blood flow (ml. per 100 Gm. per min.).
†$CMRO_2$ represents cerebral oxygen consumption (ml. per 100 Gm. per min.).
‡CVR represents cerebrovascular resistance (mm. Hg per ml. per 100 Gm. per min.).
§$(A\text{-}V)O_2$ represents cerebral arteriovenous oxygen difference (vol. per cent).
‖Data may incorporate a systematic error which raises CBF and $CMRO_2$ and lowers CVR, respectively, all by about 15 per cent. The adjusted values have been used in Figs. 1 to 3.
¶Calculated from CBF and $CMRO_2$.

Each report usually contained sufficient information to indicate that the values obtained would be representative of normal values. In five of the series the subjects were apparently normal, nonhospitalized individuals.[1,3,6,8,9] Some consisted of alert and active patients with no cardiovascular disease, hospitalized for minor elective surgery[2] or for minor illness.[4] Some groups recorded the absence of cardiovascular[2,4,10,11] and neurologic disease.[2,4,11] The two older series of Kennedy[7] consisted almost entirely of children under study because of a previous history of mild convulsive seizures; in no case had there been a seizure within several days of the procedure and none of the patients was receiving any drug therapy. Previous work in adults[13] had demonstrated no abnormalities in the functions under consideration in such patients. Schieve and Wilson[4] included a few schizophrenic patients in two of their series, but again a previous study[14] had shown no change from normal in cerebral hemodynamics or metabolism in this disease. In the oldest group[12] only one-third of the subjects were mentally alert, the remainder showing various degrees of deterioration; the mean values for the six mentally normal individuals, however, were the same as those for the series as a whole.

REVIEW OF RESULTS

The relationship between age and cerebral blood flow is presented in Fig. 1. Each point represents the mean of a series of determinations. During the first decade of life the values for both cerebral blood flow and cerebral oxygen con-

sumption are quite high, the latter representing 48 per cent of the total oxygen consumption of the child in the basal state. There appears to be a rapid fall in the over-all cerebral circulation about the time of puberty, which continues through absolescence. From the third decade onward, there is a more gradual but continuous decline in this function through middle and old age. Fig. 2 depicts a similar but reciprocal change in cerebrovascular resistance, a function

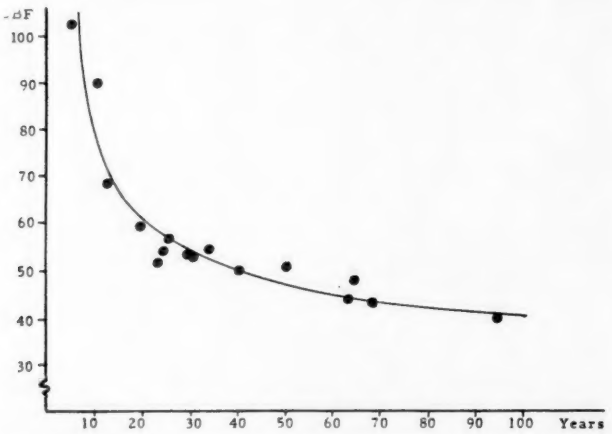

Fig. 1.—The relationship between cerebral blood flow (ml. per 100 Gm. per min.) and age in years.

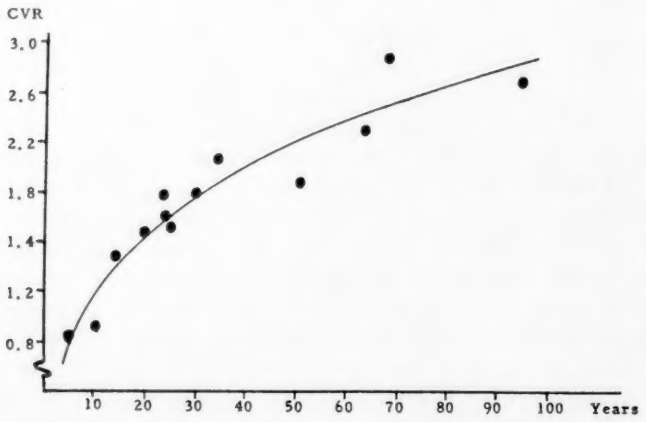

Fig. 2.—The relationship between cerebral vascular resistance (mm. Hg per ml. per 100 Gm. per min.) and age in years.

which represents the sum of all of the factors which hinder the flow of blood through the brain. The changes in cerebral oxgen consumption, expressed as milliliters of oxygen utilized per 100 Gm. of brain per minute, are given in Fig. 3. This shows similarly a rapid and then more gradual fall with advancing years.

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These findings for cerebral blood flow, oxygen consumption, and cerebrovascular resistance seem quite clear-cut; and, considering the large number of individual investigators involved, the data show relatively little scatter. Their interpretation, however, is not so definitive. One must first entertain the possibility that these changes are the result of some age dependent artifact. The values obtained by use of the nitrous oxide technique apply rigorously only to the tissues and regions which are represented in the blood at the superior bulb of one internal jugular vein. There is satisfactory evidence[1] that in most individuals such blood is representative of blood in both internal jugular veins and is only unsignificantly (less than 3 per cent) contaminated with blood arising from extracerebral sources.[17] There is practically no evidence, however, that these sources of error, demonstrably negligible in a general sample of the population, show no progressive increase with age. The effect of progressively poorer mixing of cerebral venous drainage, even if it occurred with advancing age, would not be a systematic one but could reflect iteslf only in a greater scatter of the individual data. In the other hand, a progressive increase in contamination of internal jugular blood with blood from the less well perfused and more slowly metabolizing extracerebral tissues could produce some of the changes observed. Since in the adult this contamination is less than 3 per cent, it could certainly not account for the dramatic changes observed during adolescence.

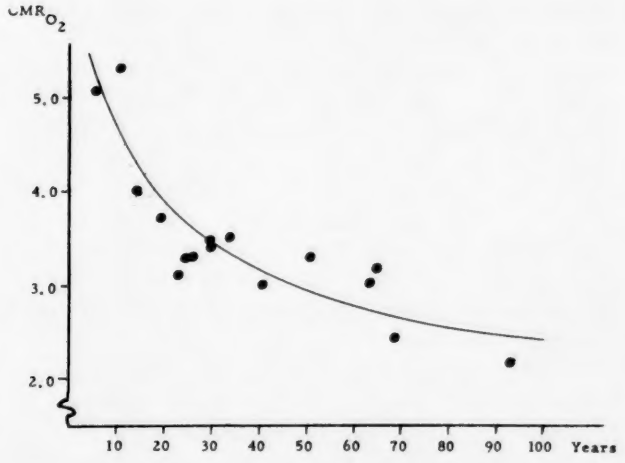

Fig. 3.—The relationship between cerebral oxygen consumption (ml. per 100 Gm. per min.) and age in years.

Furthermore, the nitrous oxide technique, as originally described, offers a means of detecting the presence of at least gross contamination. In two studies on elderly individuals performed by the original technique,[10,18] there was no evidence to suggest the presence in such patients of a degree of contamination significantly greater than that which obtains in normal young men. All of these considerations, although admittedly indirect, speak against the possibility that the

age correlation of cerebral blood flow and the other related functions is the result of an anatomic artifact.

Since there is evidence[19] to suggest that certain types of anxiety may be associated with significant increases in cerebral oxygen consumption and blood flow, it is important to consider the possibility that the unusually high values for these functions found by Kennedy and his colleagues in childhood were the result of a decreased acceptance of the procedure and a greater apprehensiveness on the part of these subjects. It is apparent that these investigators recognized this possibility and took consideralbe pains to minimize it. These included the use of a plastic "space dome" instead of a face mask, projection of animated cartoons during the procedure and refusal to continue the studies at the first sign of uncooperativeness. In the opinion of this reviewer, anxiety was held to a minium by this group as well as the others, and, in any case, was not likely to show an age dependent variability.

There is good reason to believe, therefore, that the values summarized for the various functions are a close approximation to those which exist in the normal resting state at various ages. One may formulate a number of hypotheses in an attempt to explain the changes which occur in association with age. The nitrous oxide technique yields results only in terms of unit volume or (since its specific gravity is quite constant) unit weight of brain. It does not distinguish between cellular and extracellular, active or metabolically sluggish masses. The changes, therefore, could be a reflection of a generalized decrease in the circulation to, and metabolism of, the individual actively metabolizing units or, equally well, a progressive reduction in the ratio of their mass to that of the brain as a whole. Although a decrease in neuronal density is commonly regarded as a concomitant of advancing age, the author is aware of only one quantitative study on the human brain.[20] Although this study was restricted to neuronal density in certain areas of the cerebral cortex and may not have controlled completely such artifacts as shrinkage, it is hardly likely that these could have accounted for more than a small share of the marked decrease in the average neuronal population which was found to be associated with age. The striking similarity between this curve (Fig. 4) and the curves for cerebral blood flow and oxygen consumption suggests more than a chance relationship.

Regardless of whether one or the other or both processes are occurring in association with maturation and aging, some more fundamental and age-related causes must be sought capable of affecting the metabolic activity or the survival of the active components. These findings are compatible with at least two hypotheses. The more obvious and, until recently, the generally accepted one would attribute to the circulation a primary role with metabolic and functional changes the result of aterations in the cerebral blood supply. There is no evidence that under normal circumstances an augmentation of the circulation to the brain will produce an increase in its metabolism and, therefore, little reason to attribute the high cerebral oxygen consumption found by Kennedy in childhood merely to the increased circulatory rate. On the other hand, the undeniable postulate that oxygen consumption must at some point be limited by oxygen delivery makes at least tenable the hypothesis that the decreased functional

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acuity of the aging brain is dependent upon its slowing rate of metabolism which is, in turn, the result of the progessive diminution in circulation. The common, if not invariable, finding of some degree of cerebral arteriosclerosis associated with old age, perhaps reflected in the progressive increase in cerebral vascular resistance, supports this hypothesis and, in fact, provides a reasonable mechanism for the circulatory deficit.

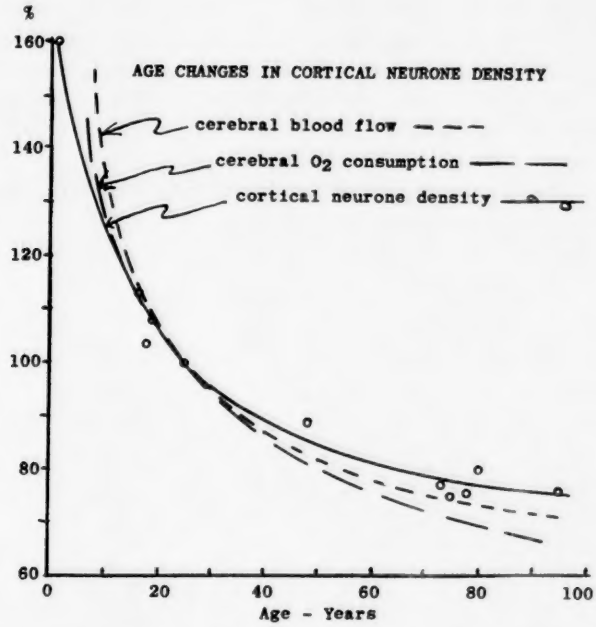

Fig. 4.—Mean values for neurone density in four areas of cortex at different ages from data of Brody.[20] The mean age curves for cerebral blood flow and oxygen consumption are included for comparison. All values are expressed as per cent of the respective mean value at the age of 25 years.

Failure to find a significant correlation between loss of mental acuity and generalized cerebral circulatory or metabolic deficit[11] does not invalidate this hypothesis since cerebral as well as general arteriosclerosis is known to be unevenly distributed, while mental acuity is so poorly localized a function as to require the destruction of a large portion of the brain before an impairment is detectable. An observation less readily reconciled with the hypothesis is the fact that there is not found a significant decrease in cerebral oxygen consumption in acutely induced anoxia[21] or hypotension[22,23] of sufficient severity to affect the mental state quite perceptibly. It is possible to argue, of course, that the circulatory deficit in aging is hardly an acute process and that metabolic sequelae may occure after many years which are not apparent within a few minutes.

More important than the soundness of the arguments against the hypothesis of primary cerebral circulatory deficit, however, is the absence of crucial evidence in its favor, and at least one alternative hypothesis must be entertained. This would postulate that a more fundamental cerebral derangement in aging lies in

the diminished metabolic demands of the brain. This could be the result of simple loss of neurons which had fulfilled their life spans, a progressive deterioration in certain essential cellular components, a decrease in neuronal interconnections and interaction, or a lessened functional demand as a result of the psychological and social changes which attend the aging process. Whatever the cause of such reduced requirements, and those listed are hardly a complete tabulation, the restricted cerebral circulation and increased vascular resistance could follow rather than cause the decreased metabolism. Whether achieved by the vasodilator effects of the products of metabolism or by some local reflex, an adjustment of the circulation to meet metabolic demand is reasonably well established in the brain as well as in other tissues. Such an hypothesis of functional and metabolic aging of the brain, independent of circulatory supply, is supported by the occurrence of some types of age-associated functional deterioration in cetain species like the rat which do not develop arteriosclerosis.

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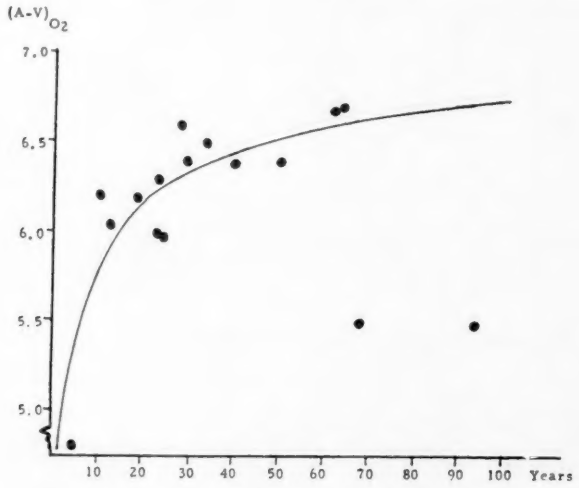

Fig. 5.—The relationship between cerebral arteriovenous oxygen difference (ml. per 100 ml.) and age in years.

The distinction between a primary circulatory and a primary metabolic or functional deficiency in the aging brain, although of considerable pertinence to an understanding of senility and to rational attempts to retard or ameliorate it, cannot be made definitively on the basis of present data. A possibility is presented, however, of obtaining some indication of the real sequence of events by means of the cerebral arteriovenous oxygen difference. This quantity can readily be shown to vary inversely with the ratio of cerebral blood flow to cerebral oxygen consumption so that this measurement, although conveying no information with respect to either blood flow or metabolism separately, is an accurate measure of the relationship between them. In all cases where there is a primary reduction in cerebral circulation, such as hyperventilation[21] or an acute fall in blood pressure,[22,23] there is a significant increase in cerebral arteriovenous oxygen

difference while this value is consistently low in those states such as anesthesia,[24] diabetic,[25] or insulin coma[14] where the primary depression is clearly in cerebral oxygen demand. Unfortunately, the behavior of the cerebral arteriovenous oxygen difference in senescence is equivocal (Fig. 5). Although the data as a whole show a tendency toward a widening of this arteriovenous difference, suggesting a greater circulatory than metabolic involvement, two of the series are markedly aberrant. It is quite possible that a primary circulatory deficit may, if sufficiently severe and chronic, produce intracellular changes resulting in an overriding decrease in metabolism and thus obscure the analysis in later stages of the process. This factor, in addition to the presence of severe anemia, which also causes per se a reduction in the cerebral arteriovenous oxygen difference, probably contributed to the ambiguity of some of the measurements reported. This concept, however, if applied to more carefully selected subjects, may provide a greater insight into the dynamics of aging in the brain.

SUMMARY

A review of available information on over-all cerebral blood flow and oxygen consumption in man obtained by means of the nitrous oxide technique reveals a distinct correlation of these functions with age.

There is a rapid fall in the circulation and oxygen utilization of the brain from childhood through adolescence followed by a more gradual but progressive reduction throughout the remaining age span.

The factors responsible for these changes and whether one or the other is primary appear to be suitable subjects for continued investigation.

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BRAIN METABOLISM IN RELATION TO AGING

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THERE is a general agreement that an impairment in the efficiency of mental as well as of physical powers occurs in old age. In some, this impairment is delayed longer than in others and in any case the difference is less noticeable in individuals whose intellectual capacities are well developed. What are the underlying changes in the brain which may give rise to such deteriorating alterations? It will be the main purpose of this paper to ascertain the biochemical changes in the brain associated with old age in an effort to correlate them with the alterations in behavior which may occur in the last period of life.

One method of study is to measure the cerebral metabolic rate. Long years of experience have proved that basal metabolic rate, or the oxygen consumption of the entire body, gradually falls after 40 years of age and more swiftly so after 80 years. There is evidence that cerebral metabolic rate also declines in old age.

For the sake of completeness and to set the background for further discussion we shall reiterate that cerebral metabolic rate is reduced in aged individuals.[1] The decrease in metabolism is dependent chiefly upon a retardation of cerebral blood flow and the latter is associated with an augmented cerebral vascular resistance.[2,3] Why is this retardation of blood flow not compensated for by a relaxation of cerebral vascular resistance? It has been shown that even in the aged, cerebral blood flow can increase significantly when there is a drug-induced fall of systemic blood pressure and at that time cerebral vascular resistance is reduced.[4] Why then does not the aged individual correct his slow cerebral blood flow by a compensatory relaxation of cerebral-vascular resistance? There would seem to be another factor, perhaps that of parenchymal damage, and the diminished oxygen consumption of the brain would then be secondary to alterations in brain cells.[5] Thus the cells may not only suffer injury as a result of the impaired blood supply but there may be a direct action on the cells by some toxic product so that parenchymal damage may accrue. In that case the low cerebral metabolic rate could be secondary to prior damage of the brain cells. It is of interest that there seems to be a similar decrease of metabolic rate whether or not the patients reveal abnormal behavior.[6] Aged individuals who are apparently normal have cerebral metabolic rates like those of elderly persons with

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signs of psychotic or neurologic disorders. Whether or not the regressive changes are associated with clinical manifestations or are relatively silent depends upon the part of the brain where they are most prominent. In any event a decrease of brain metabolism is a sign of aging and further support for this conclusion comes from observations of excised cerebral tissues. The examination of brain metabolism in the various mammalian forms reveals a rapid postnatal rise followed by a slower and more gradual fall during the period of maturity. This applies to the rat[7-9] and the dog[10] (Fig. 1). Unfortunately, none of these data was extended far enough into the life span to include the old age, and for an obvious reason; it is more difficult to get aged laboratory animals than younger ones.

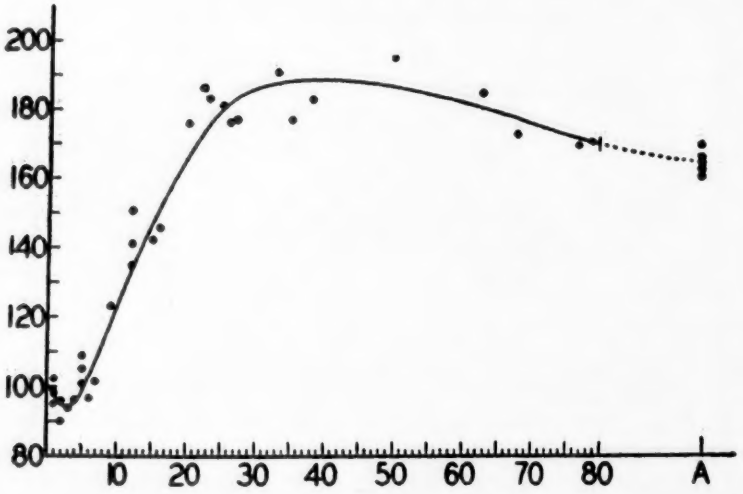

Fig. 1.—Changes in oxygen consumption of rat brain from birth through maturity. Age in days (abscissa) plotted against oxygen uptake, cubic millimeters 0_2 per 100 mg. tissue per hour (ordinate). Brain metabolism rises rapidly to a maximum at 1 month of age, after which there is a slight but significant decrease (From Tyler and van Harreveld, Am. J. Physiol. 136:600, 1942).

There is, however, one report in the literature[11] which estimates brain metabolism in the rat throughout a period of three years. This is a ripe old age for that animal. Unfortunately in this paper the oxygen consumption was reported on a basis of dry weight. Although this method is frequently used it misses many of the variations of the early rapid rise of cerebral metabolic rate. This failure is easily understandable, since the water content rapidly falls at this time so both dry weight and oxygen consumption rise together. Only on a moist weight basis can we observe the variations in the rates of metabolism per weight of brain tissue. When changes in water content are taken into consideration, cerebral metabolic rate is given in terms of the living tissue, i.e., in the terms of brain weight similar to those observed in vivo. Despite this drawback in the method of estimating the oxygen consumption on a dry weight basis, a fall of metabolism after two years of age is evident in Reiner's observations. In fact in the aged rats the cerebral metabolic rate has been reduced to such low values as are seen only in embryonic life (Table I).

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TABLE I. RESPIRATION OF RAT BRAIN HOMOGENATES IN RELATION TO AGE

AGE (MONTHS)	Embryos	0–1	2–4	4–6	6–12	12–18	18–24	Greater than 24
QO_2 DRY WEIGHT	10	14	15	16	15	16	15	10

(From Reiner, J. Gerontol. 2:315, 1947.)

TABLE II. WATER PER CENT OF RAT BRAIN IN RELATION TO AGE

DAYS	Birth	10	21	31	41	100	250	365
PER CENT OF WATER	88.00	86.72	82.49	80.19	79.36	78.55	78.01	77.50

(From Donaldson.[12])

If we accept a reduction in cerebral metabolic rate as an accompaniment of old age, we may regard it as another sign of altered biochemistry and seek other changes of the brain which can be correlated with such a decrease. Let us turn first to an examination of the water content of the brain. One of the most important constituents of the body in general, as well as of the brain, is water. Certainly, it is greatest from a quantitative viewpoint, and all the reactions on which life depends take place in an aqueous medium. Donaldson published observations on rats showing a decrease in the percentage of water content for the entire brain in the first year of life (Table II). Other experiments made on rabbits up to 4 years of age, approximately middle life, are in agreement with such a decrease in moisture.[13] In addition, they disclose that the water content of the various parts of the brain examined reveal a phyletic order. The newer parts of the brain, cortical gray and caudate nucleus, contain more moisture on a percentage basis than the superior colliculi and medulla oblongata. These results, suggestive as they are, fail to give us information on what happens in human beings.

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TABLE III. TOTAL NITROGEN CONTENT (GRAMS PER CENT) OF FOUR DIFFERENT AREAS OF CEREBRAL GRAY MATTER OF PATIENT B, AGE 69 YEARS, AND OF HEMISPHERES OF FOUR RABBITS

		PATIENT	RABBIT HEMISPHERES
Frontal Pole	R	1.56	1.70
	L	1.44	1.74
Other Frontal Area	R	1.44	1.71
	L	1.33	1.71
Temporal Pole	R	1.39	1.70
	L	1.54	1.72
Occipital Pole	R	1.64	1.70
	L	1.88	1.75

At this point it may be well to emphasize that observations made on human beings do not afford experimental conditions as satisfactory as those of animal experiments, let alone the fact that these brains have been frequently obtained from diseased patients and have undergone premortal changes including those of a period of coma before death. In addition, post-mortem alterations must be considered, for rarely is a brain taken immediately after death, and the periods before autopsy are variable. Furthermore, in the presentation of these data, mention was not made of which cortical areas were sampled. Yet, observations performed in this laboratory[14] disclose that the chemical contents of the cerebral cortex are not uniform but may vary from part to part (Table III). It may be seen that not only do the nitrogen contents of different cortical areas vary but also symmetrical parts taken from the right and left hemispheres differ. These

results differ from those obtained on rabbit brain, for in that animal the correspondence for the right and left sides is close. You will observe that the total nitrogen contents of the right and left hemispheres of four different rabbits are in much closer agreement than those of the right and left sides of the human patients (Table III). The data on human brains therefore must be evaluated in terms of the conditions in which they were obtained.

The work of Johnson, McNabb, and Rossiter[15] shows that the human adult brain exhibits a smaller concentration of water than that of the infant and that the decrease in water concentration is associated with the growth of the total lipids of the brain. Unfortunately, these results do not yield information on our particular subject of interest, old age. The data of MacArthur and Doisy,[16] unlike the preceding, include exact ages but go only as far as 67 years. The observations of Brante,[17] however, extend to the brains of individuals up to 90 years of age. Brante presents the values for the dry weight as per cent of wet weight, of cortical gray and white matter (Table IV). Subtracting these

TABLE IV. WATER CONTENT OF CORTICAL GRAY AND WHITE MATTER, PER CENT FRESH TISSUE, IN RELATION TO AGE

YEARS	1	2–5	10–16	19–55	65–76	78–90
			Gray			
NO. OF BRAINS	2	3	4	2	4	3
WATER PERCENTAGE	89	87	84	84	86	87
			White			
NO. OF BRAINS	3	3	4	4	3	2
WATER PERCENTAGE	85	75	69	71	71	74

(Calculated from Brante.[17])

results of dry weight per cent from 100, we obtain the per cent moisture content of the brain. In Table IV the results obtained from individuals of various age groups are averaged in an attempt to determine whether there is a trend in the changes of water content with age. A rapid fall in water content from the first year of life to about 10 to 16 years of age is followed by a stage of stabilization with, however, a rise in the percentage of water in the brains of the oldest individuals studied. We wish we had more data to test the idea as to whether the brain contains a greater concentration of water in extreme old age or, stated differently, suffers a decrease in solids. With additional information we might find that the water content of the brain remains practically unchanged. It is even possible that a fall in the water content of the brain occurs. But we must take the available observations into consideration, and it is therefore necessary to determine whether any relationship exists between the lipids of the brain

and water, as the lipids form a quantitatively important fraction of the dry weight of the brain.

In order to compare Brante's[17] lipid data with those of water, the former are also recalculated on a moist weight basis. Table V contains such a recalculation of Brante's work and is in accordance with the same age groups as in Table IV. If attention is focused on total lipids, it is seen that there is a gradual rise, first fairly rapid, and then slower to 65-76 years, followed by a decrease from 78-90 years. In general the lipid contents of gray and white matter show the same order of alterations except that the concentrations of lipids in white matter are greater and the differences between the various ages are more marked. Table V includes not only the total lipids but phospholipids, cholesterol, and cerebrosides; and again a rise to 65-76 years of age and a fall thereafter is noted.

TABLE V. LIPIDS OF CORTICAL GRAY AND WHITE MATTER, PER CENT FRESH TISSUE, HUMAN BRAIN, IN RELATION TO AGE

YEARS	1	2–5	10–16	19–55	65–76	78–90
Gray Matter						
NO. OF BRAINS	2	3	4	2	4	3
TOTAL LIPIDS	3.47	4.62	4.98	5.31	5.60	4.65
PHOSPHOLIPIDS	2.14	2.68	3.12	3.28	3.12	2.50
CEREBROSIDES	0.36	0.51	0.36	1.04*	0.70	0.68
CHOLESTEROL	0.54	0.70	0.75	0.80	0.81	0.68
White Matter						
NO. OF BRAINS	3	3	4	4	3	2
TOTAL LIPIDS	7.54	13.66	18.72	18.00	18.10	15.10
PHOSPHOLIPIDS	3.81	6.12	8.22	7.79–	7.49	6.82
CEREBROSIDES	1.36	2.90	4.46	4.07	4.22	3.24
CHOLESTEROL	1.50	3.04	4.50	4.93	5.01	3.67

(Recalculated from Brante.[17])
*One value.

Thus there is an early rapid increase of the various lipids followed by a slower one and finally a reversal in old age. The changes in total lipids are the converse of those in water. Such an agreement might be expected since calculations for water and for lipids were made on the basis of the total weight of the brain tissue studied. We are brought back to the same point discussed under the heading of moisture content of the brain, namely, we need additional data to determine whether or not the apparent hydration of the brain will be supported by further work.

Germane to our discussion is the division between extracellular and intracellular water. In 1916 Donaldson[18] wrote of the unique character of the nervous system to accumulate the greater fraction of its lipids outside the cell bodies in the form of myelin substances. Thus, while extracellular fluid decreases the

relation between water and solids within the cell remains fairly constant. The data obtained by Yannet and Darrow,[19] on growing cats, yield quantitative results in support of Donaldson's conclusions. They found that the reduction in concentration of water, which occurs with growth, is due to a decrease in extracellular fluids. Extracellular water decreases from 33.9 to 29.8 per cent, while intracellular water remains unchanged within the error of the method, going from 50.7 to 51.0 per cent. Accordingly, they note that sodium and chloride, largely extracellular elements, decrease, while potassium, mainly an intracellular substance, remains unaltered (Table VI). Yannet and Darrow[19] also note that the increase of nitrogen and phosphorus is chiefly dependent on the greater concentration of lipids.

If the suggested hydration in old age is accompanied by a reduction in the concentration of total lipids, and if the former is chiefly extracellular, then the inverse relationship between lipids and extracellular water observed during growth may also hold for old age and the extracellular fraction may increase at that time. However, without available data on the inorganic metabolism of the aged brain and its water compartments, such a decision between extracellular and intracellular fluids cannot be drawn. To recapitulate, during the growth of the organism all elements forming the brain expand, but on a percentage basis some increase at the expense of others. We have seen that the concentration of lipids becomes larger as the total fluids fall; and this fall of fluids is due chiefly to a decrease in the extracellular component. Whether or not a reversal of this relationship takes place in the aged individual cannot be determined without additional data.

Another important factor in the total solids of the brain is its proteins. The increase of total brain protein during the early part of the life span is seen in Table VII. These data are accurate but they are not carried far enough to draw conclusions on the changes in protein in old age and, moreover, they were obtained on rats. Observations of human brain are supplied from the results of MacArthur and Doisy.[16] We see again a rise throughout the life period, almost reaching maximal values in the 21-year-old adult and decreasing somewhat in the 67-year-old individual (Table VIII).

A source of information on the protein concentration of the cerebral cortex is found in Brante's work.[17] Protein content can be estimated from the differences between the weight of total lipids and the total dry weight. Such values, representing as they do all materials not soluble in fat solvents, will include total acid-soluble substances, but since these are relatively constant[16] we may assume differences are due to fluctuations in protein* (Table IX). A steady increase of protein from 1 year to the 19-55-year period is observed both in gray and white matter, followed by a regression which occurs during the last two periods indicated in the chart. Observations of proteins are of special interest, since enzymes have protein moieties. A diminution in protein may be associated with a lesser concentration of enzymes and some may grow while

*The values for protein are free of contamination with lipid nitrogen because that substance was extracted by lipid solvents. They do, however, fail to include proteolipids which were extracted along with the lipids.[20]

TABLE VI. CONCENTRATIONS PER KILO OF BRAIN TISSUE OF WATER, NITROGEN, CHLORIDE, SODIUM, POTASSIUM, PHOSPHORUS, AND FAT

GROUP	NO. OF CATS	WATER (gm.)	NITROGEN (gm.)	CHLORIDE (mM)	SODIUM (mM)	POTASSIUM (mM)	PHOSPHORUS (mM)	FAT (gm.)
A	9	84.6 ± 5.0	14.7 ± 0.3	43.2 ± 1.4	55.1 ± 1.4	87.0 ± 1.6	76.9 ± 3.7	30
B	8	80.8 ± 4.0	16.8 ± 0.2	39.0 ± 1.0	52.5 ± 1.2	88.0 ± 2.2	96.3 ± 0.5	60

(From Yannet and Darrow, J. Biol. Chem. 120:467, 1937.)
Group A includes animals weighing up to 800 grams; Group B, animals weighing from 800 to 2,500 grams.

TABLE VII. RAT BRAIN PROTEIN (ABSOLUTE WEIGHT IN MILLIGRAMS) IN RELATION TO AGE IN DAYS

DAYS	1	10	20	40	120	210
MILLIGRAMS	15.14	60.45	119.40	136.00	165.20	177.00

From Donaldson.[12]

TABLE VIII. TOTAL PROTEIN IN PERCENTAGE OF FRESH TISSUE HUMAN BRAIN IN RELATION TO AGE

FETUS		INFANT			ADULT			
3 MO.	7 MO.	1 MO.	3 MO.	8 MO.	21 YR.	33 YR.	35 YR.	67 YR.
3.77	3.98	4.57	5.29	6.09	8.03	8.11	8.99	7.53

(From MacArthur and Doisy.[16])

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others decay. For that reason the measurement of the protein does not give us information on direction of change in any specific enzyme. Yet it is suggestive that proteins do decrease in old age at the same time that cerebral metabolic rate undergoes impairment.*

TABLE IX. ESTIMATED PROTEIN CONTENT OF CEREBRAL GRAY AND WHITE MATTER, PER CENT FRESH TISSUE HUMAN BRAIN, IN RELATION TO AGE

YEARS	1	2–5	10–16	19–55	65–76	78–90
			Gray Matter			
NO. OF BRAINS	2	3	4	2	4	3
ESTIMATED PROTEIN CONTENT	7.08	8.34	10.89	12.00	8.51	8.39
			White Matter			
NO. OF BRAINS	3	3	4	4	3	2
ESTIMATED PROTEIN CONTENT	7.62	11.57	10.96	11.60	10.90	10.40

(Calculated from data of Brante.[17])

Within recent years, new micro methods have been developed for the examination of protein within a single cell. The study of the absorption spectrum of a single nerve cell area containing nucleic acid is some measure of its protein content, for PNA (pentose nucleic acid) forms a pentose nucleoprotein. The maintenance of normal neuronal function is associated with the production of pentose nucleoprotein, and large amounts of that complex substance are found in the large nerve cell of the adult. What is significant for the present study is that the amount of PNA decreases with old age.[22] X-ray microradiography reveals that the parts of the brain containing pentose nucleoprotein possess much less dry matter than areas containing a yellow pigment, a substance which accumulates in old age. Thus the nucleoproteins are fading away at the time when the yellow pigment is increasing. These data are, of course, of an entirely different order from those obtained by the older methods and it is difficult to compare the two results. But taking all observations, chemical and histochemical, into consideration, it may be said that the possibility of a decrease of protein in old age is suggestive. Probably cells do not diminish in size.[23] On the other hand, morphologic evidence discloses that all cortical layers show a diminution in cell numbers with age and such changes are in agreement with a decrease of protein.[23,24] According to Brody[23] and others, neuronophagia is not limited to extreme old age but goes on throughout most of the life period. Not only cell bodies[23,24] but also the myelinated processes disappear.[25] Thus

*Despite a decreased quantity of brain protein the quality remains relatively constant as indicated by the essentially unchanged amino acid composition.[21]

both intracellular neuronal materials and extracellular myelinated substances are depleted. As previously discussed, it seems logical that the extracellular water compartment enlarges in a compensatory manner.

We have mentioned a yellow pigment or yellowish-brown pigment which appears in the human central nervous system in increased amounts as the individual grows older. Apparently its rate of destruction is slower than that of production. This interesting sign of aging has been studied systematically in dogs from 2 to 17 years of age.[26] When the central nervous system cells as well as the peripheral nervous system cells of dogs are stained by the periodic acid-Schiff reagent, three kinds of stained material are seen in the cytoplasm of the nerve cells: glycogen, granular, and nongranular substances. Neither the granular nor the nongranular stained portions are observed in dogs under 10 years of age, while all animals over 12 years of age reveal these two substances, both of which increase with age. The nongranular material reveals the histochemical reactions of mucopolysaccharide attached to a protein. Thus it is assumed to be a mucoprotein. The granular substance gives the reactions of a lipochrome, a pigmented fatty substance. It is present in the autonomic ganglia, sensory ganglia, Purkinje cells of the cerebellum, dorsal root cells, and the cortical pyramidal cells. This material found in dogs is of special interest because it is identical with that observed in aged human beings. The first traces of the yellow pigment may be seen in children 6 to 7 years of age and later the yellow pigment becomes widespread throughout the central nervous system as life proceeds.[22] It appears in the motor nerves, motor-root cells, the pyramidal cells, and in the sensory and sympathetic ganglia cells. This yellow granular matter is present in large amounts in the cytoplasm of an increasing number of cells with aging. It is not associated with any pathologic changes, for the function of the central nervous system does not seem to be altered by its presence. So far it appears to be simply one of the many signs of aging.

Finally, we should like to present some results obtained in our laboratory which have not been previously published[14]: values for glutamic acid, glutamine, pyruvic acid, and alpha-ketoglutaric acid of the brain throughout the life span of the rat, including values up to 2½ years of age (Fig. 2). We may observe in the first place that pyruvic acid and alpha-ketoglutaric, two intermediaries of energy metabolism constantly occurring in the brain, reveal a fall in the first 10 days of life, after which there is a stabilization of their concentrations throughout the remainder of the life span. Such a relative constancy indicates the continuous necessity for these reactions to maintain life. Glutamine exhibits an early fall in contrast to glutamic acid which rises rapidly during postnatal life. These substances attain maximal values during maturity; glutamate earlier, glutamine later, and they reveal consistent decreases subsequently. The reduced concentrations of these substances in old age do not prove that the brain is hydrated at this time, but such changes are compatible with that possibility.

In conclusion, we may say that the biochemical data for the brain in old age is sparse. Additional studies should be made using not only the well-known chemical methods for the various solid constituents of the central nervous sys-

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tem but also the newer histochemical techniques. The results suggest diminished amounts of solids in the central nervous system, both in lipids and proteins, in old age. If this suggestion is sustained by further work, then the decrease in protein is compatible with that of the cerebral metabolic rate observed in old age.

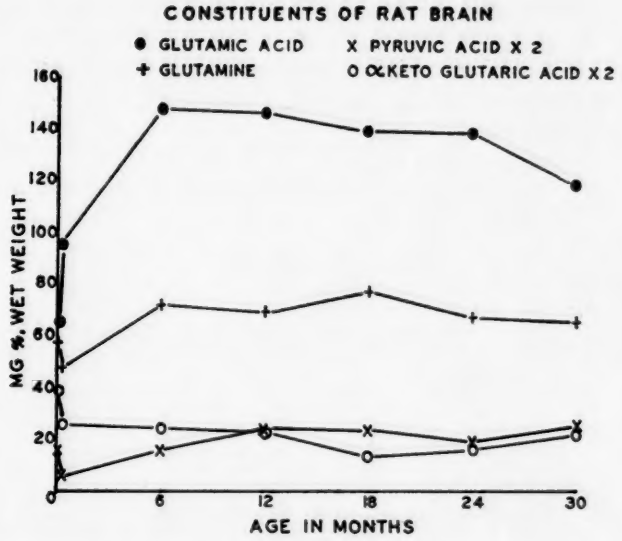

Fig. 2.—Constituents (milligram per cent) of rat brain from birth to 2½ years of age.

The studies of the brain in fetuses and newborns have revealed the rapid changes which take place at that time. Quantitative studies made at later periods seem to disclose a more static condition. And yet we know that this is only relatively so; there is a constant interchange going on, so that if the total concentration of a brain constituent apparently remains the same, it is simply due to the fact that the rate of production is approximately equaled by the rate of destruction. The observations made with the aid of absorption spectra support the results obtained by chemical measurements of the various constituents of the brain and yield added evidence that even in old age changes in these constituents are going on at a fairly rapid rate.

In early life, production gets ahead of destruction and growth occurs. In extreme old age the reverse seems to be true as the solid parts decrease. Change must be regarded as part of life!

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A FOLLOW-UP STUDY OF TUBERCULOSIS IN FORMER STUDENT NURSES

I. Methods of Locating and Obtaining Information From a Study Population of 25,752

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IS IT feasible in this country to undertake epidemiologic studies that require many years of observation on a widely dispersed study population of many thousands of persons? Will the number who are "lost" from observation or who refuse to cooperate be so large and possibly so selected as to invalidate conclusions drawn from such studies?

Follow-up studies, of course, do not represent a new approach in medical and public health research. Many of those undertaken in the past have been of great importance in helping to define and resolve numerous problems in the control of acute communicable diseases. Few, however, have involved the large numbers of persons, the wide geographic coverage, and the long periods of observation needed for studying some of the chronic, less well-defined diseases and disabilities that today are rapidly becoming the chief concern of public health.

The etiology and predisposing factors of many chronic diseases are still poorly understood: some apparently begin in childhood and do not become manifest until later life; some appear to be influenced by geographic, racial, and socioeconomic factors; some, of great interest, are not highly prevalent in the population. Among the follow-up investigations undertaken in the past on various aspects of chronic diseases, well-known examples would include the Framingham Demonstration[1] begun in 1916; the Hagerstown Health Studies[2]; the studies in Cattaraugus County, New York[3]; and in the Eastern Health District of Baltimore.[4] Those studies, and later ones, have been fundamental in establishing patterns for long-term investigations, particularly of general population groups. Much less experience is available as guidelines for follow-up investigations in populations that are widely dispersed geographically, or that

This is the eighth in a series of reports on a study of tuberculosis in student nurses, aided by a grant from the Committee on Medical Research of the American Trudeau Society, medical section of the National Tuberculosis Association.

become dispersed between periods of observation where the problems of locating persons after intervals of years or even decades become a matter of critical concern. The size of this country, the mobility of its people, and the absence of a system for registering a person's movements make the task of carrying out such studies seem very great.

The present paper deals with techniques used and problems encountered in an attempt to trace and get information from nearly 26,000 young women who had participated some years earlier in a nation-wide cooperative study of tuberculosis in student nurses. The earlier study, which began in 1943 and continued until 1949, included the students enrolled in 78 schools of nursing located in ten different metropolitan areas throughout the country. While in school, the students were examined periodically for early signs of tuberculous infection and disease. No systematic attempt had been made to keep in touch with them after they left school until, late in 1951, the decision was made to undertake a follow-up study—to attempt to locate all of the former student nurses and to determine how many of them had had tuberculosis or had died of the disease. Although the initial objective of the follow-up was thus to learn more about tuberculosis, the decision to try to make the follow-up 100 per cent complete led to an important secondary objective—to learn as much as possible about the problems of finding and getting information from a fairly large and widely dispersed group of young adults a number of years after they had last been observed.

The follow-up has been surprisingly complete. Of the 25,752 former student nurses in the study, only 9 have not been located; and only 44 of the 25,743 who were located did not wish to give the information requested of them. In short, between July, 1952, and October, 1954, 99.97 per cent of the study population was located and 99.83 per cent cooperated.

THE EARLIER STUDY AND THE FOLLOW-UP POPULATION

Details on the scope and methods of the earlier study of tuberculosis in student nurses are given in a number of previously published papers.[5-11] The schools in the cooperative study program included most of the nurses training centers located in and around Baltimore, Columbus (Ohio), Denver, Detroit, Kansas City, Los Angeles, Minneapolis, New Orleans, Philadelphia, and San Francisco. Schools with both large and small enrollments were included. The students came from rural as well as urban homes; and many of them were residents of the states in which the schools are located, although some were from adjacent or distant states, some even from abroad. As a whole, the group under observation was probably fairly representative of the young white women who were taking nurses training in the years between 1943 and 1949 in the United States.

All students enrolled in each of the cooperating schools of nursing were included in the earlier study, the total group placed under observation during the six-year period reaching more than 30,000. As a substantial proportion of the students dropped out of training after only a few weeks or months, particularly during the war years, it was decided not to include in the group to be followed

those who stayed in training for less than six months. It was also decided not to include those who started training in the fall of 1949 shortly before the study was discontinued. And, for the sake of greater homogeneity in the follow-up group, some 373 students attending two training schools for Negroes were also excluded. No other selective criteria were applied, as shown in Table I.

TABLE I. POPULATION IN THE STUDY OF TUBERCULOSIS IN STUDENT NURSES

Population in earlier study (1943-1949)	30,476
Excluded from the follow-up	4,724
In training less than 6 months	1,929
Entered training in fall of 1949	2,422
Students in schools for Negroes	373
Population in follow-up study (1952)	25,752

Information about the character of the population when they were under observation as student nurses and after an interval of several years when the follow-up had been completed is given in summary form in Tables II-VI, Table IX, and Fig. 1. The total number of students enrolled in the cooperating nursing schools in each of the ten metropolitan areas ranged from around 1,800 in Colum-

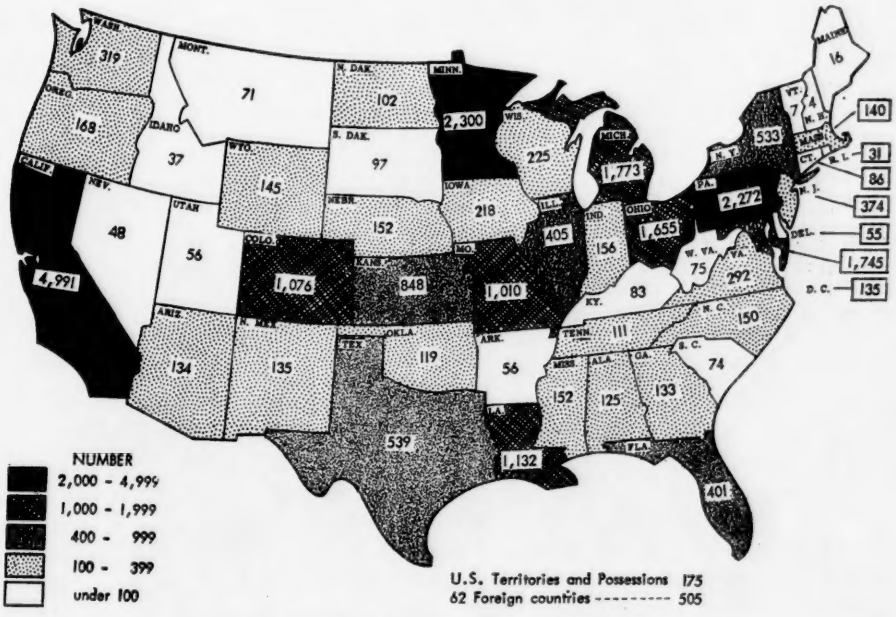

Fig. 1.—Place of residence of former student nurses at time of follow-up.

bus, Denver, and San Francisco to nearly 4,000 in Minneapolis. Two-thirds of the students first came under observation during the three-year period 1943-1945 and almost the same proportion were last observed during the three years 1947-1949. About three-fourths of the students were between 18 and 21 years of age when they came into the study and the same proportion between 23 and 29 years at the time of the follow-up in 1952. By that time, too, three-fourths of the

TABLE II. FOLLOW-UP POPULATION BY METROPOLITAN AREA IN WHICH THE NURSES TRAINING SCHOOLS ARE LOCATED

METROPOLITAN AREA	NUMBER OF SCHOOLS	NUMBER OF STUDENTS	PER CENT
Baltimore	10	3,286	12.8
Columbus	5	1,874	7.3
Denver	12	1,796	7.0
Detroit	3	2,148	8.3
Kansas City	11	2,603	10.1
Los Angeles	12	2,946	11.4
Minneapolis	9	3,909	15.2
New Orleans	3	2,167	8.4
Philadelphia	5	3,196	12.4
San Francisco	6	1,827	7.1
Total	76	25,752	100.0

TABLE III. FOLLOW-UP POPULATION BY YEAR FIRST AND LAST OBSERVED IN THE EARLIER STUDY, 1943-1949

YEAR	NUMBER		PER CENT	
	FIRST OBSERVED	LAST OBSERVED	FIRST OBSERVED	LAST OBSERVED
1943	5,313	222	20.6	0.9
1944	6,163	2,067	24.0	8.0
1945	5,768	3,244	22.4	12.6
1946	2,365	4,260	9.2	16.5
1947	2,869	5,224	11.1	20.3
1948	2,736	3,592	10.6	13.9
1949	538	7,143	2.1	27.8
Total	25,752	25,752	100.0	100.0

group were married and a high proportion of them had children; more than four-fifths had completed their nursing training; and all but a small fraction of the graduates had been engaged in the practice of their profession for at least one year. They had become widely scattered since their student days, although nearly two-thirds of them were still living in the same state, about one-third had moved to another state and the remaining several hundred had become dispersed throughout the United States territories and possessions and 62 foreign countries.

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TABLE IV. AGE OF FOLLOW-UP POPULATION WHEN FIRST OBSERVED IN THE EARLIER STUDY, 1943-1949, AND AT TIME OF FOLLOW-UP, 1952

AGE (YEARS)	NUMBER		PER CENT	
	FIRST OBSERVED	AT FOLLOW-UP	FIRST OBSERVED	AT FOLLOW-UP
17	1,204	—	4.7	—
18	7,242	—	28.1	—
19	6,062	1	23.5	0.0
20	4,508	2	17.5	0.0
21	2,770	269	10.8	1.0
22	1,484	1,615	5.8	6.3
23	754	2,011	2.9	7.8
24	481	2,184	1.9	8.5
25	321	3,026	1.2	11.8
26	188	3,572	0.7	13.9
27	172	3,633	0.7	14.3
28	133	3,044	0.5	11.9
29	102	2,317	0.4	9.0
30	65	1,526	0.3	6.0
31	58	890	0.2	3.5
32	58	443	0.2	1.7
33	41	288	0.2	1.1
34	34	213	0.1	0.8
35 and over	75	613	0.3	2.4
Total	25,752	25,647*	100.0	100.0

*Excludes 96 deceased and 9 not located.

TABLE V. YEARS OF POST-GRADUATE NURSING PRACTICE OF THE FOLLOW-UP POPULATION BY YEAR OF GRADUATION

YEARS OF NURSING PRACTICE	YEAR OF GRADUATION										
	Total	1943	1944	1945	1946	1947	1948	1949	1950	1951	1952
0	925	4	39	85	134	138	103	55	104	125	138
1	3,960	10	112	226	310	389	334	219	421	1,710	229
2	4,155	18	158	265	438	562	547	376	1,474	317	—
3	3,414	21	160	287	394	613	646	1,040	253	—	—
4	2,923	21	145	237	400	662	1,299	159	—	—	—
5	2,623	11	133	260	493	1,455	271	—	—	—	—
6	1,582	12	114	259	966	231	—	—	—	—	—
7	826	11	137	529	149	—	—	—	—	—	—
8	444	12	323	109	—	—	—	—	—	—	—
9	98	42	56	—	—	—	—	—	—	—	—
Unknown	429	4	31	55	66	73	53	31	42	53	21
Total*	21,379	166	1,408	2,312	3,350	4,123	3,253	1,880	2,294	2,205	388

*Excludes 63 deceased.

OUTLINE OF PROCEDURES

From the medical point of view, the primary objective of the follow-up study was to identify those in the population who had had tuberculosis or had died of it. Ideally, that objective might be achieved by having a complete medical

history and physical examination, chest x-ray, tuberculin test and, perhaps, other tests for each person. In order to determine the feasibility of getting such data, and also to test methods of locating persons, several pilot studies were carried out in 1951 and early 1952 when detailed plans for the follow-up study were being formulated.

TABLE VI. COMPARISON OF ADDRESSES FOR A SAMPLE OF THE FOLLOW-UP POPULATION WHEN FIRST OBSERVED IN EARLIER STUDY AND AT TIME OF FOLLOW-UP

ADDRESS	NUMBER	PER CENT
Same address	1,300	12.5
Same city	1,626	15.7
Same state	3,299	31.8
Different state	3,913	37.7
Different country	236	2.3
Total	10,374	100.0

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Results of the first pilot studies indicated that relatively few of the former students had any knowledge or signs of having had clinical tuberculosis, and those who did seemed entirely willing and able to give pertinent details about their illness. It also became clear that the task of trying to obtain comparable data from physical examinations or even to get current chest x-rays of *all* the women in order to supplement their medical histories would be tremendously difficult, and expensive. The decision was therefore made to try to screen out the few who had had tuberculosis by the use of a questionnaire sent directly to all of the former students. And, as Frost[12] observed some years ago, there were reasons to believe that cooperative informants would to the best of their knowledge give fairly accurate information.

Thus, the first step in the follow-up study was to contact each former student nurse by mail and ask her to fill out a questionnaire. But before taking that step, pilot studies were made to try out different forms, to test the response by mail, to devise record systems, and the like. After some experimentation, the questionnaire reproduced in Fig. 2 was adopted. Though brief and easy to complete (we thought), the answers were expected to serve several purposes: first, to furnish details for the accurate identification of each person; second, to provide information that might have a bearing on tuberculosis; third, to give the names and addresses of two persons through whom she might later be traced; and finally, to screen out the group requiring further study through the key question: "Has any examination ever indicated that you might have had or now have tuberculosis?"

LOCATING THE FORMER STUDENT NURSES

In order to send a questionnaire by mail to each of the former students, an address more recent than her "permanent" address when in training school, four to ten years earlier, was found to be necessary. The study population consisted entirely of young women who, when first observed in the earlier study,

PLEASE PRINT CLEARLY

DEPARTMENT OF HEALTH, EDUCATION, AND WELFARE
~~FEDERAL SECURITY AGENCY~~
PUBLIC HEALTH SERVICE

QUESTIONNAIRE FOR FORMER STUDENT NURSES

NAME _____ DATE OF BIRTH _____
(First) (Middle) (Maiden) (Married) (Month) (Day) (Year)

PRESENT ADDRESS _____
(Number) (Street) (City) (State)

HUSBAND'S NAME _____ NUMBER OF CHILDREN _____ DATE OF ENTRY TO NURSES TRAINING _____
(First) (Middle) (Month) (Year)

HAS ANY EXAMINATION EVER INDICATED THAT YOU MIGHT HAVE HAD OR NOW HAVE TUBERCULOSIS?

NAME OF SCHOOL _____

LENGTH OF TIME ENGAGED IN NURSING SINCE LEAVING TRAINING.
CIRCLE NUMBER OF YEARS:

YES		UNCERTAIN		NO	

0 1 2 3 4 5 6 7 8 9

IN ORDER THAT IT MAY BE POSSIBLE TO REACH YOU IN CASE YOU MOVE, PLEASE LIST THE NAMES AND ADDRESSES OF TWO RELATIVES OR FRIENDS MOST LIKELY TO KNOW YOUR WHEREABOUTS

NAME	MAILING ADDRESS	RELATIONSHIP

PHS-1826 (CDT)
(7-52)

U. S. GOVERNMENT PRINTING OFFICE 16—66830-1

Form approved.
Budget Bureau No. 68-5012.1.

Fig. 2.—Questionnaire used to screen the follow-up population.

were in training for a profession. Although few were married at that time, many of them would undoubtedly marry during the following years and, as a consequence, change their names and their places of residence. The group as a whole could also be expected to be a mobile one. Certainly they were at an age for moving about and, in addition, opportunities for moving would probably be much greater than for a nonprofessional group of corresponding age. Moreover, many of the students were completing their training during the later war and early postwar years when their services were needed by the armed forces in various parts of the world.

The first task in starting the follow-up was therefore to obtain the current mailing address of each former student; and several sources of information were available. First, during the earlier study in 1943-1949 each student had been asked (in anticipation of a later follow-up study) to fill out a form which, among other things, asked for her permanent address and the names and addresses of three relatives or friends likely to know her whereabouts after she left school. Another source was the nurses training schools the women had attended; many of the schools tried to keep in touch with their former students, particularly through their alumnae associations. Still another source was the American Nurses Association which, in 1951, had carried out a nation-wide survey of registered nurses; and information they had obtained included the current (or recent) address and both the maiden and married names of those who had replied. Thus, by writing directly to the training schools and alumnae associations, and by matching our records with those of the American Nurses Association's 1951 survey, current addresses were obtained for a large number of the former students.

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The first batch of several thousand questionnaires was mailed in July, 1952, followed by successive batches during the following months. A preferential system was set up for deciding which address to use when more than one was obtained for the same person. In general, an address obtained from the 1951 Survey of Registered Nurses was considered the most recent and therefore preferable to an address supplied by the school or alumnae association. If no address had been obtained from either source and a "permanent" address had been given by the former student in either 1948 or 1949, that address was tried. For those who had given their permanent addresses before 1948, as well as those for whom our initial letter was returned unclaimed, the relatives or friends were contacted by letter for the women's present whereabouts. Finally, the small group for whom no current address became available had to be handled in whatever way seemed most appropriate.

In a good many cases where the available sources provided no current address, useful leads were obtained from the personnel files of the nursing schools. Original applications for admission to the school, letters requesting transfer of credits to other schools or colleges, the name and place of employment of parents, high school attendance before entering training, names of employers before (or after) the period in training, character references, church membership while in training—such information often provided the first clue to successfully tracing a former student.

On-the-spot investigations often proved essential to track down or follow new leads, and for this purpose a fruitful source of help was a commercial credit

company. The particular one whose services were obtained is a nation-wide company with representatives in almost every city and town in the United States and with reciprocal agreements with similar organizations in many parts of the world. Such companies avail themselves of many different sources of information, including credit records, and also make use of city directories that list the current resident of each address. Thus their local representatives could request information by telephone or by visiting the present residents of homes previously occupied by the nurses, their relatives, or friends. Moreover, the world-wide coverage available to some companies makes it possible for leads to be followed from place to place in order to locate a person.

Some of the difficult-to-locate cases had to be traced through miscellaneous other sources, such as the Department of National Defense, State Boards for Nurses Registration, State Offices of Vital Statistics, State Vehicle Registration Departments, former classmates and employers, pretraining schools, postoffices, and so on. We simply followed whatever leads we could find in trying to locate the women, as illustrated by the following brief accounts of how some of them were finally found:

Through a former maid, information was secured about the city of residence, the pregnancy of the nurse, approximate month of childbirth, and the first name but not the surname of the husband. Using the maiden name of the nurse, the records of the vital statistics office were checked, the birth certificate for the child was located, and the nurse's married name and address were obtained.

The only information available was that the nurse's sister, whose name was known, had married a soldier during World War II in Seattle. The records of the vital statistics office in Seattle were checked and the marriage certificate was located. Attached to the marriage certificate was a telegram from the father of the bridegroom giving approval to the marriage. The latter, contacted in a small Kansas town, provided the information that his son and daughter-in-law were living in Juneau, Alaska, but they had not communicated with him in recent years. The telephone directory for Juneau provided the exact address of the sister, who in turn was able to supply leads as to the present whereabouts of the nurse.

It was known that the nurse was born in one of several counties of an eastern state. The area was predominantly rural and the nurse had a very unusual maiden name. The local representative of the credit company was requested to contact by phone the few other residents in the area bearing the same name. After several fruitless contacts, one was found who knew the family and provided leads as to their present residence.

Only the maiden name of the nurse was available, but information was obtained through a former landlady that the nurse and her husband were in the entertainment business and appeared frequently on TV with their trained animal. Through this lead it was discovered that the nurse was the co-owner of a well-known TV "animal personality."

It was learned that the father of the nurse had served in World War I and had died from war injuries some time later. It was considered probable that his widow might be receiving a service-connected compensation and, therefore, the Veterans Administration branch office of their former permanent state residence was contacted, the claim records searched, and the mother found to be a claim beneficiary residing with her daughter and son-in-law.

The nurse, in early childhood, had attended a parochial boarding school in a small Canadian town. On the assumption that there might be a particular attachment to this distant school, the school was contacted. By coincidence and good luck, the school supplied the information that the parents of the girl had visited the school in recent months while motoring through Canada and had left their current address with them.

The only lead obtained was that an old address of the nurse's brother was a rooming house for medical students. The records of the nearby medical college were searched in vain. On the possibility that he may have attended another school, the American Medical Directory was consulted and a listing was found for a person with the same name and initials who recently had been graduated from a medical school. He was finally traced through the Department of National Defense after a lead indicated that he was in the Armed Services. Through him, his sister's address was obtained.

Of the nine women who were not located, it seems reasonable to believe that most of them could have been traced had the available leads been followed further. None of the nine had been graduated from nursing school—all had spent less than two years in training. Several seemed to be burdened with more than their share of personal problems and had an understandable desire for anonymity: one had vanished after abandoning her children; another had been arrested for assault with intent to kill; one was involved in family conflicts and had severed relations with her parents; and two were in serious marital difficulties culminating in desertions. Because of such circumstances, and the fact that we had little difficulty in learning about the death of 96 former students, it seems unlikely that any of the nine who were not located are dead.*

Thus, a total of 25,743 out of the 25,752 former students were located during the follow-up. Slightly more than half, or about 13,500, were located through addresses they had given either for themselves or for their friends or relatives at the time they were in training school. Some 43 per cent were located through addresses obtained from their training schools, alumnae associations, or the 1951 Biennial Survey of Registered Nurses. Of the remaining group of more than 1,200, over 700 were found through the credit company and about 500 through various other sources.

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OBTAINING ANSWERS TO THE QUESTIONNAIRE

As the main objective of the follow-up was to get information about tuberculosis morbidity and mortality in the study population, the task of locating the former student nurses was superseded in importance only by the problem of getting the questionnaires answered and returned.

The routine procedure was to send the questionnaires by regular mail, accompanied by the letter reproduced in Appendix A. The letter attempted to enlist the former student's cooperation by explaining briefly and directly why she was being sent the questionnaire. It recalled her participation in the earlier study when she was in training, and told her that she was now being called upon for a follow-up phase of that study. Her answers would be treated as confidential. An addressed, franked envelope was enclosed for returning the questionnaire.

If no response was received within five weeks, a brief reminder letter was sent together with a copy of the first letter and a questionnaire. Early in the program a second reminder was usually mailed five or six weeks after the first reminder if still no reply had been received. However, it soon became apparent that the second reminder had little effect, so it was replaced by a personal letter, recalling the exact dates the former student nurse had participated in the earlier

*One of the nine has now been located and has filled out the questionnaire.

study and giving the proportion of her classmates who had already responded to the questionnaire. The letter also asked if she had any questions or complaints that might be behind her hesitancy to respond. It was often sent air mail and, for the small number where difficulty was anticipated, by registered or special delivery mail.

In general, about 65 per cent of the study population responded within a few weeks after receiving the first letter and questionnaire, the peak in response being reached in about ten days. The first reminder letter brought the total response up to nearly 88 per cent and the second, a more personal reminder, to around 95 per cent.

For a group of about 1,200 former students who failed to reply to any of the three letters, no routine procedure could be followed; for each case the next step was governed by what we knew (or suspected) was the reason no reply had been received. In a few instances the person was known to be traveling and had no permanent address. If there was reason to expect that she would remain inaccessible for some months, her parents or a close friend whose name she had given as a reference was asked to fill out the questionnaire for her. In instances where the permanent address was known to be correct but the woman apparently did not want to respond (in some cases she had written that she would not respond), a Public Health Service nurse attempted to interview her either by telephone or in person. The nurse would then explain the background and purpose of the follow-up study and thereby induce her to answer the questionnaire. In other instances, where a personal reminder was all that was thought necessary, a field representative of the commercial credit company was asked to contact the woman by telephone or by a visit to her home. He was instructed not to attempt to explain the objectives of the study but simply to tell her that her response would be appreciated. In some instances, former students who had written that they were very much interested in the study were asked to make the contact for us.

As shown in Table VII, the questionnaires were filled out by 99.2 per cent of the former student nurses themselves. For the remaining 0.8 per cent, where

TABLE VII. SOURCE OF INFORMATION FOR THE FOLLOW-UP QUESTIONNAIRES

SOURCE	NUMBER	PER CENT
From the former student nurse herself	25,550	99.22
Directly by correspondence	24,401	94.76
Through Public Health Service field staff	778	3.02
Through commercial credit agency field staff	371	1.44
From other sources (relatives, institutions, friends, etc.)	193	0.75
No indication of unwillingness to reply	53	0.21
Indication of unwillingness to reply	44	0.17
Deceased	96	0.37
Information not obtained (person not located)	9	0.03
Total	25,752	100.00

the information was obtained from other sources, one-half were for women who had died, about one-fourth were for those who preferred not to cooperate, and the rest were for women who either were traveling or in institutions and were unable to answer for themselves.

Table VIII shows that 75 per cent of the questionnaires, excluding those obtained in the pilot studies, were received within the first six months, nearly 90 per cent within nine months and 95 per cent within one year. In connection with the table it should be noted that the work of getting addresses for the large-scale follow-up had begun early in 1952, after completion of the first pilot studies, and the first large batch of questionnaires was sent out in July. Altogether, it took about two years to get addresses and completed questionnaires for over 99 per cent of the total population.

TABLE VIII. DATE OF RECEIPT OF FOLLOW-UP QUESTIONNAIRES

DATE	NUMBER	CUMULATIVE	
		NUMBER	PER CENT
1952			
July–Sept.	5,912	5,912	23.7
Oct.–Dec.	12,689	18,601	74.6
1953			
Jan.–Mar.	3,751	22,352	89.6
April–June	1,424	23,776	95.3
July–Sept.	864	24,640	98.8
Oct.–Dec.	203	24,843	99.6
1954			
Jan.–Oct.	108	24,951	100.0
Total	24,951*		

*Excludes 696 in pilot study, 96 deceased and 9 not located.

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FACTORS AFFECTING RESPONSE TO THE QUESTIONNAIRE

Although information about the time it took to obtain completed questionnaires from the former student nurses cannot be separated from the time consumed in trying to locate them, it may nonetheless be relevant to consider whether some of the characteristics of the study population were associated with early or late response to the questionnaire. Table IX summarizes certain pertinent findings.

So far as age is concerned, the response from the younger women appeared to be as prompt as that of the older ones. Graduate nurses were somewhat more prompt than those who had dropped out of training before being graduated, although the difference is small and may only reflect the fact that current addresses were less difficult to obtain for the graduates than the nongraduates; a higher proportion of the graduates were unmarried and consequently had not changed

their names, and more complete records were available for them from the training schools, alumnae associations, and other professional sources. The married women tended to be less prompt than the unmarried ones and those with children slower than those without children.

TABLE IX. CHARACTERISTICS OF FOLLOW-UP POPULATION BY DATE OF RECEIPT OF QUESTIONNAIRE

CHARACTERISTICS	NUMBER	DATE						
		1951	1952		1953			1954
		PILOT STUDIES	JULY-SEPT.	OCT.-DEC.	JAN.-MARCH	APR.-JUNE	JULY-DEC.	
FOLLOW-UP POPULATION*	25,647	2.7	25.8	75.2	89.9	95.4	99.6	100.0
Age in 1952								
20-24	6,082	1.3	25.3	75.2	90.0	95.7	99.7	100.0
25-29	15,592	2.9	25.6	75.4	90.1	95.6	99.6	100.0
30-34	3,360	3.8	26.8	74.3	88.8	94.5	99.3	100.0
35 and over	613	5.4	28.1	75.9	88.6	93.3	99.8	100.0
Graduate status								
Graduate	21,379	2.9	27.8	78.2	91.6	96.4	99.7	100.0
Nongraduate	4,268	1.7	15.6	60.8	81.4	90.7	99.0	100.0
Marital status								
Single	6,199	4.2	30.0	78.8	91.1	95.5	99.6	100.0
Married	19,448	2.2	24.4	74.1	89.5	95.4	99.6	100.0
Number of children								
0	4,878	0.0	24.5	75.8	89.9	95.6	99.6	100.0
1	6,069	0.1	23.8	75.7	90.9	96.4	99.7	100.0
2	5,429	0.1	22.1	72.6	88.9	95.1	99.5	100.0
3	1,940	0.1	18.5	67.9	86.4	93.7	99.5	100.0
4 and over	473	0.2	15.6	62.2	81.2	91.1	97.9	100.0
Unknown	659	63.7	72.3	86.1	92.5	95.1	99.7	100.0
Screened as possible tuberculosis cases	531†	4.9	26.9	79.3	89.8	93.6	98.5	100.0
Deceased‡	96	34.4§	61.5	72.9	95.8	99.0	100.0	100.0

*Excludes 96 deceased and 9 not located.
†Excludes 6 deceased.
‡The date reflects when information about fact of death was obtained.
§Information for these deaths was obtained largely from school records during previous years and not as a result of the pilot studies.

Finally, the table shows that information was obtained as promptly from the small group screened out as possible tuberculosis cases and for those who had died as for the remainder of the study population. After nine months, for example, questionnaires were still lacking from about 10 per cent of the entire study population and also from 10 per cent of those screened as possible tuberculosis cases, and knowledge of the fact of death for less than 5 per cent of the 96 persons who had died.

Many intangible factors may have affected favorably the willingness to respond. Interest and good-will are possibly two such factors. Another may be that cooperation was requested of a professional group whose training and, presumably, whose interests, too, were directed toward matters of health. The view taken in writing to them was that they would appreciate (and respond to) a brief but direct statement about why the follow-up was being undertaken. Immediately upon receipt of a questionnaire a personal thank-you note was sent to each former student. Letters of inquiry from them for further details about the study were answered promptly and fully. In short, every effort was made to maintain (or establish) a somewhat personal relation with the former students whose further contribution to the study was being requested.

The circumstances under which a small proportion of the former students had left training were no doubt responsible for their showing no great enthusiasm for cooperating in the follow-up study. There were other reasons, too, as illustrated by the following brief accounts of how in some instances the reluctance was overcome, in others it was not:

A strongly worded letter from the nurse stated that her mother, whose address we were using, was very upset by our letter, particularly by the initials CDT-FR-D on the self-addressed envelope enclosed with the questionnaire. Her mother interpreted the cryptic initials to mean *Civil Defense Training-Field Reserve* and feared that her daughter would be drafted into the Army. The explanation that in reality the initials identified our office: *Chronic Disease and Tuberculosis Division, Field Research Branch, Diagnosis Section* brought immediate relief—and an immediate response.

She was an itinerant ecdysiast eking out a bare existence from her profession. Repeated attempts to contact her had failed; though voices often could be heard from inside her apartment, the doorbell was never answered, and on the door itself were several notes from bill collectors, such as, "Return the $40.00 or will call the cops." When finally confronted she admitted trying to avoid people because of her many creditors. "I'm even afraid of the Public Health Service—I'm sure I owe them something." She willingly completed the questionnaire.

In some cases, however, the husband or other relative appeared to be responsible for the woman's refusal:

One indicated that her husband had gone over the questionnaire, was very suspicious of our inquiries about her marital status, number of children, and years of nursing experience. He thought this was not a tuberculosis survey but had something to do with the Army—preparation for drafting nurses into service. He would not allow his wife to answer the questionnaire.

In another case, the mother told us that her daughter had remarried and was overseas with her new husband. She refused to give us the daughter's married name and address and did not want the girl to have any contact with the Public Health Service as she feared communication with us might encourage the girl to return to nursing. "Furthermore", the mother added, "my daughter had considerable trouble with her former husband and I don't want him to find out where she is."

And in a few instances the intention was perfectly clear but the reason behind it was not:

"I have received all your questionnaires and I have thrown them away as I have no intention of giving out any information. I refuse to answer any questions and want nothing to do with your project."

"I know very little about tuberculosis and nursing in general and do not wish to sign any forms."

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Lest the impression be gained that our letters and questionnaires provoked many unpleasant reactions, it should perhaps be recalled that the "reluctant" group constituted only a very small proportion of the total study population. Most of the former students responded promptly and willingly; often, the questionnaires were accompanied by comments, such as the following:

"Do not hesitate to contact me if there is any further information you desire. May I offer best wishes in the success of your studies."

"Thank you for bearing with me, and if there is any other information which you may need, please don't hesitate to write. I will try to be more prompt next time."

"Sorry for the delay in sending you the completed questionnaire. . . . . The first one was eaten by my baby."

"Thank you very much for your prompt and interesting reply. I'm always interested in the work you are doing, and will be more than happy to cooperate in any way that I can."

"After graduation I started sending a Christmas letter to Mrs.————, our retired superintendent of nurses, with a brief summary of my classmates' activities during the year. This has turned into an interesting class history and has kept the class close together even though some are now in foreign lands. I have most of the current names and addresses of the class. . . . If I can be of any assistance please let me know."

"Thank you for your letter informing me how I was located by your agency. . . . In an agency as large as the USPHS it is nice to know someone would take time out to answer a curious question. Good luck in tracing 26,000, rather 25,999 now!"

SECONDARY SCREENING OF THE FOLLOW-UP POPULATION

As the first large group of completed questionnaires was being returned, it was found that about 10 per cent of the replies to the key question on whether they might have had tuberculosis was either affirmative or doubtful. Some had supplied additional information by writing above the check mark that they had received treatment or were currently under treatment for tuberculosis; a fair number, however, had simply added the words "positive tuberculin," "contact with a case of TB," "pulmonary calcification," etc. The questionnaire had been intended to screen out only those in whom tuberculosis would have had to be considered in the differential diagnosis of an illness, not those whose only evidence of tuberculous infection was a positive tuberculin reaction or the like. A pilot study was therefore undertaken to find out what proportion of those answering *Yes* or *Uncertain* fell into the latter group. As the proportion was found to be high the decision was made to ask *all* those who answered in the affirmative (or doubtful) to explain why they had done so. In other words, a secondary screening would be made of the 10 per cent who answered the questionnaire by checking *Yes* or *Uncertain* to select for further study only those who could reasonably be considered possible cases of tuberculosis.

First, however, a search was made through the health records of each student—both those which had been obtained during the years she was in training as well as those received later from the schools and other sources. Records for all persons who had had diagnostic examinations or treatment of any kind for possible tuberculosis were matched against the entire file of completed questionnaires—those on which *No* had been checked as well as those checked *Yes* or *Uncertain*. By that process several hundred persons were identified who clearly

fell within the critical group requiring further study and to whom, therefore, there was no need to send the secondary questionnaire.* The remainder, a total of about 2,000 whose records contained nothing suggesting tuberculous disease, were sent the secondary questionnaire reproduced in Appendix B and the accompanying letter in Appendix C.

Answers to the secondary questionnaire were received from almost 95 per cent of the women within five months. Reminder letters were sent; telephone calls and personal visits were made as before when necessary. About 5 per cent of the group had to be retraced to obtain current addresses. And a response of 100 per cent was achieved in less than a year.

Altogether the follow-up work, including the secondary screening, resulted in the screening out of a group of 537 former student nurses to be studied further as possible cases of tuberculosis. Detailed information pertinent for the study of tuberculosis morbidity has now been obtained for all of the 537; and that phase of the follow-up took about six months. The field work for the entire follow-up program was thus completed by August, 1955.

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BASIC RECORD FILES FOR THE FOLLOW-UP

The work of the entire follow-up extended over a period of nearly four years, beginning with the first pilot studies late in 1951 and ending in the fall of 1955 with the detailed study of the small group screened out as possible cases of tuberculosis. During the course of this work over 100,000 letters were sent to the former student nurses, their relatives, and so on, and the volume of incoming letters was almost as large. The task of handling that volume of mail, of managing the clerical and field operations, and of processing the material required, among other things, the setting up of two basic record files. First, a 5″ x 8″ card was prepared for each former student to include identifying data, her permanent address, and the names and addresses of the references she had given while in training. To this card was added any information obtained about the former student's present whereabouts as well as a chronologic record of all letters sent and received, and other pertinent data. The cards were filed by a serial number that identified the person and the school she had attended. All letters, questionnaires, etc., were marked with that serial number, as matching of numbers rather than names made it easier to bring together documents pertaining to the same person. (A cross-reference name file was also set up as an adjunct to the numerical file.) As soon as the questionnaires were processed they were stapled to the cards and transferred to a "completed" file; the remaining "incomplete" file thus represented a current estimate of the extent and character of the pending load.

The second basic record file was made up of IBM punch cards. A card prepared for each person in the study population summarized the data from the records of the earlier study and the additional information received on the questionnaires. The cards in this file provided details for assessing the quality and

*All but 20 of that group had answered the initial questionnaire by checking *Yes* or *Uncertain*. Those 20 were sent the secondary questionnaire to check the validity of their answers.

possible selectivity of the responses obtained at any given interval during the follow-up work; they also served as a source of basic data for analyzing the results of the study.

DISCUSSION

The present paper illustrates, we believe, that all but a very few persons in a large and widely scattered study population can be traced and will cooperate in a follow-up study a number of years after they were last under observation. Partly because of our inexperience and partly because so little has been written on the matter, we encountered a good many problems and made mistakes which, in retrospect, point toward several ways of increasing the efficiency of a follow-up.

First, and perhaps almost too obvious: plans for the follow-up should be a part of the initial design for a long-term study. Details may be difficult to foresee, of course, but every effort should be made to anticipate the follow-up phase instead of waiting to make specific plans (as we did) when the time comes to do the follow-up.

Second, it is clear from our experience that one of the most critical matters is to obtain from each study participant the names and addresses of several persons who can be expected to know her whereabouts in the future. Although the former student nurses in the present study were asked for three such references, it is now apparent that it would have been preferable to have specified adult *male* relatives or friends, and to have asked for the occupation as well as the name and address. (As men's names rarely change, those established in a profession or business can often be located through occupational or city directories.[13]) In addition to such references for the study participant, the father's full name, address, and occupation, and the mother's maiden name, may furnish important clues in later tracing an individual.

Third, although we decided in the present study to try to locate and get information from each person in the follow-up population, it would probably be sufficient in similar studies to sample those who do not readily respond or who cannot be traced through the usual routine. Thus, a fair amount of time and expense might be saved by taking a randomly selected one-half or one-third of the 5, 10, or 20 per cent that remains after the bulk of the follow-up population has responded.

Fourth, on the matter of screening out a special group in the follow-up population, it is now apparent that in framing a questionnaire as much attention must be paid to the negative as to the positive side of key questions. In the present study, our attention was primarily focused on screening out all persons who could possibly be suspected of having had tuberculosis. We failed to recognize that the key question could also be answered in the affirmative by a substantial number of persons without the slightest suspicion of tuberculous disease. The penalty was the need to do a secondary screening. Although it is difficult to see even now how that might have been avoided, it would have been possible to have included the secondary questionnaire with the initial one, with a request that only those who answered the key question in the affirmative need fill out the secondary questionnaire.

Finally, the kind of follow-up study described in the present report cannot be attempted without a well-trained field staff. But, unless that staff is specifically trained in the techniques of locating persons and, further, unless sufficient time and money is available for the travel involved in following leads from place to place, the services of a central agency that makes a business of locating persons through a network of experienced field representatives is unquestionably a more efficient and more economical way to do certain aspects of a follow-up. The potentialities of utilizing the services of such an agency have hardly been explored in medical research work; but our experience suggests that more of the work of tracing persons and related nonmedical tasks as, for example, making personal contacts to stimulate response to a questionnaire, securing photostatic copies of death certificates for those who have died, and so on, can be satisfactorily handled by certain commercial agencies.

The growing importance of chronic diseases in public health today and the attendant recognition of the need for long-range planning of research studies in large population groups give relevance, we believe, to the practical problems involved in locating and obtaining health data from a study group after intervals of many years. As discussed in a conference on "Methods in Public Health Research,"[14] persons "lost" from observation cannot simply be disregarded in analysis of the results of a study, although the problem of how to deal with them seems to be difficult to solve satisfactorily. While our experience is limited to a special kind of population, it would appear that persons can be located and will cooperate in a follow-up study; the number who are "lost" need not necessarily constitute more than a negligible proportion of the total follow-up population.

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SUMMARY

With present-day interest rapidly turning toward the chronic diseases and disabilities, investigations calling for observations on large numbers of persons for periods of time measured in decades rather than years or months, will undoubtedly become an increasingly prominent feature of public health research. And for the kinds of investigations that require wide geographic coverage or involve study populations which become widely dispersed before the follow-up is completed, the practicability of being able to trace individuals successfully becomes a question of immediate concern. The present paper bears directly on that question, and indicates that persons "lost" from observation, even in a large study population, can be reduced to a negligible number.

The present paper, the eighth in a series on the study of tuberculosis in student nurses, describes the methods used to locate and obtain information in the follow-up of a widely scattered population of 25,752 former student nurses, after an interval ranging from four to ten years since they had last been observed in an earlier study. All but nine were located, and only 44 did not wish to answer the questions put to them.

Experience in the present study brings out a number of problems and mistakes which, in retrospect, point toward ways of making a follow-up study more efficient. One of the most critical in anticipating a follow-up is to obtain from each study participant the names and addresses of several persons, pre-

ferably adult male relatives or friends, through whom the participant may later be traced. Second, it is probably sufficient in many studies of this kind to take a fair-sized random sample of the final 5, 10, or 20 per cent of the total study population that are difficult to locate or do not readily respond. And finally, the present kind of follow-up cannot be attempted without a well-trained field staff, experienced in methods of tracing persons.

APPENDIX A

INITIAL LETTER REQUESTING COMPLETION OF QUESTIONNAIRE

DEPARTMENT OF
HEALTH, EDUCATION, AND WELFARE
PUBLIC HEALTH SERVICE
Washington 25, D. C.

Perhaps you will recall that, while you were in nursing school, you participated in a tuberculosis study of student nurses. From that program have come many valuable contributions to our knowledge about tuberculosis and much assistance in the problem of tuberculosis control.

You may also remember how frequently your instructors pointed out the importance of follow-up in public health studies and how often the value of these investigations suffers from the lack of later adequate health records on those who take part in them.

The Public Health Service again comes to you for assistance in this study. We urgently need your help in the form of answers to the few questions on the attached form. Please return it to us as soon as possible in the enclosed envelope which does not require any postage. Your answers will, or course, be treated in the strictest confidence.

While we want you to know how much we shall appreciate your help, we know that your greatest satisfaction will come from your knowledge that you are contributing to information which will affect the health of unknown thousands of people.

May I wish you every success and happiness in your present work.

Sincerely yours,

CARROLL E. PALMER, M.D.
Field Research Branch

APPENDIX B

QUESTIONNAIRE USED FOR SECONDARY SCREENING

DEPARTMENT OF
HEALTH, EDUCATION, AND WELFARE
PUBLIC HEALTH SERVICE

FOLLOW-UP STUDY OF FORMER STUDENT NURSES

Reasons for checking "YES" or "UNCERTAIN" to the question:
"HAS ANY EXAMINATION EVER INDICATED THAT YOU MIGHT HAVE HAD OR NOW HAVE TUBERCULOSIS?"

	Check Applicable Item(s)
1. I am now being treated for tuberculosis	☐
2. I have been treated for tuberculosis	☐
3. X-rays taken before, during, or after nurses training indicated *shadows* or *spots* on the lung (other than healed lesions or calcifications)	☐

4. Some of my chest X-rays showed *healed lesions* (scars). At the time these films were interpreted (or after subsequent films) there was no active tuberculosis present and the films were reported as *essentially negative*. . . . . ☐
5. Some of my chest X-rays showed *calcified areas*. At the time these films were interpreted (or after subsequent films) there was no active tuberculosis present and the films were reported as *essentially negative*. . . . . ☐
6. A *positive skin test* before, during, or after training was the basis of my reply. All my chest X-rays have been reported *essentially negative*. . . . . ☐
7. I have been exposed to one or more cases of active tuberculosis and have no knowledge as to whether I might have contracted the disease. However, all my chest X-rays have been reported *essentially negative*. . . . . ☐
8. Not having had a recent X-ray I could not give a definite reply, but to my knowledge I have never had tuberculosis. . . . . ☐
9. The answer should have been "No". I have no reason to believe that I ever have had or have been suspected of having tuberculosis. . . . . ☐
10. Other (including types of tuberculosis not affecting the lungs)

_____

_____

Name _____

Address _____

(If your address has been changed, please correct the above.)

IF ADDITIONAL SPACE IS NEEDED, PLEASE USE THE REVERSE SIDE OF THIS FORM

APPENDIX C

LETTER REQUESTING COMPLETION OF QUESTIONNAIRE USED FOR SECONDARY SCREENING

DEPARTMENT OF
HEALTH, EDUCATION, AND WELFARE
PUBLIC HEALTH SERVICE
Washington 25, D. C.

I know that you, as one of the participants, will be interested in the progress made in our follow-up of former student nurses. Even though we had had no contact with some of the girls since 1943, nearly all of the 26,000 participants have returned completed questionnaires. This success reflects the spirit of cooperation on the part of the group and their unselfish interest in health research. The apparent delay in contacting you for the next phase of our project is due to our efforts to locate and secure questionnaires from the entire study group.

The present phase, a request for the completion of the enclosed supplementary form, is limited to a relatively small segment of the original 26,000 girls. You may recall that one of the questions on the form you already submitted was: "*Has any examination ever indicated to you that you might have had or now have tuberculosis*?" In order to simplify the answers, the replies were limited to: "Yes", "Uncertain" or "No". In the attached form we are attempting to secure more definite information from those who replied "*Yes*" or "*Uncertain*" to the above question.

We are perhaps imposing on you by this additional request. We have listed what may be considered the major reasons for the replies on the original questionnaire, so that it will take but a few minutes of your time to complete the attached form. In most instances, only check marks will be necessary. However, do not hesitate to be more explicit and to use the reverse side of the form for a fuller explanation.

Thank you in advance for completing and returning the enclosed form. The success of our project depends on your continued cooperation.

Sincerely yours,

CARROLL E. PALMER, M.D.
Field Research Branch

ACKNOWLEDGMENT

We would like gratefully to acknowledge the contribution to the follow-up study of tuberculosis in student nurses made by the former student nurses themselves, their relatives and friends, the Directors and staffs of the cooperating schools of nursing, the alumnae associations, and the American Nurses Association. The follow-up study included former students from the following 76 schools of nursing:

CALIFORNIA

Fresno—Fresno General
Los Angeles—California, Glendale, Good Samaritan, Huntington Memorial, Los Angeles County General, Methodist, Presbyterian, Queen of Angels, St. Joseph's, White Memorial
Oakland—Highland, Samuel Merritt
Santa Barbara—Knapp College
San Francisco—French, Mt. Zion, St. Mary's, University of California

COLORADO

Colorado Springs—Glockner-Penrose, Memorial
Denver—Children's, Denver General, Mercy, Presbyterian, St. Anthony's, St. Luke's, University of Colorado
Pueblo—Corwin, Parkview, St. Mary's

KANSAS

Kansas City—Bethany, Providence, St. Margaret's, University of Kansas

LOUISIANA

New Orleans—Charity, Southern Baptist, Touro

MARYLAND

Baltimore—Franklin Square, Johns Hopkins, Maryland General, Mercy, St. Agnes, Sinai, South Baltimore General, Union Memorial, University of Maryland, Women's

MICHIGAN

Detroit—Henry Ford, Grace, Harper

MINNESOTA

Minneapolis—Abbott, Fairview, Minneapolis General, Northwestern, St. Mary's, Swedish, University of Minnesota
St. Paul—Ancker, Miller

MISSOURI

Kansas City—General No. 1, Independence, Research, St. Joseph's, St. Luke's, St. Mary's, Trinity Lutheran

OHIO

Columbus—Grant, Mt. Carmel, Ohio State University, St. Francis, White Cross

PENNSYLVANIA

Philadelphia—Pennsylvania, Philadelphia General, Presbyterian, Temple University, University of Pennsylvania.

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HERITABLE DISORDERS OF CONNECTIVE TISSUE

VIII. Concluding Comments

Introduction; Fibrodysplasia Ossificans Progressiva; Osteopoikilosis; Léri's Pleonosteosis; Paget's Disease of Bone; Other Possible Hereditary and Generalized Disorders of Connective Tissue; The Future in the Study of Heritable Disorders of Connective Tissue; General Summary and Conclusions

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(Received for publication Feb. 20, 1956.)

A. Introduction

IN ADDITION to the five disorders which have already been discussed and which seem clearly to be generalized and hereditary disorders of connective tissue, other conditions were investigated in a preliminary manner for the propriety of including them in this general group. The disorders so studied can be grouped in the following manner as to the more or less likelihood of their generalized and hereditary character:

I. *More Likely.*
   1. Fibrodysplasia ossificans progressiva.
   2. Osteopoikilosis.
   3. Léri's pleonosteosis.
   4. Paget's disease of bone.
   5. Cutis laxa (not to be confused with the Ehler-Danlos syndrome).

II. *Less Likely.*
   1. Localized and limited to one specialized type of connective tissue.
      a. Dupuytren's contracture.
      b. Peyronie's disease.
      c. Group of asceptic necrosis syndromes.
   2. Probably limited to one specialized variety of connective tissue (although generalized in that tissue).

Based on work supported in part by a grant-in-aid from the National Institutes of Health, U. S. P. H. S.

Reprints of this entire series of articles, appearing in successive issues of the Journal, will be available through the publishers in book form following appearance of the last installment.—Editor.

a. Osteopetrosis.
b. Achondroplasia.
c. The Morquio-Brailsford syndrome.
d. Lipomatosis.
e. Neurofibromatosis.
f. Keloidosis.
g. Multiple hereditary exostoses.
h. Ollier's enchondromatosis.

3. Too generalized (e.g., epithelial as well as connective tissue elements affected).
   a. Werner's syndrome.
   b. The Ellis-van Creveld syndrome (chondroectodermal dysplasia).
   c. Hereditary osteo- and arthrodysplasias with dystrophy of the fingernails.
   d. Chondrodystrophy with Pelger-Huët anomaly of leukocytes.
4. Although generalized and involving connective tissue elements, doubtful that hereditary.
   a. Arthrogryposis multiplex congenita.
   b. Urticaria pigmentosa.
5. Mooted whether site of basic defect is elastic fibers of skin, i.e., precise defect unestablished: Epidermolysis bullosa hereditaria.
6. Connective tissue involved only secondarily in metabolic aberration.
   a. Gout.
   b. Alkaptonuria (ochronosis).

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B. Fibrodysplasia Ossificans Progressiva

HISTORICAL NOTE

The name *myositis ossificans progressiva* is said[40] to have been assigned to this condition by von Dusch in 1868. The designation in which fibrositis is substituted for myositis has been used more frequently in recent decades[15,30,45b] since the primary change is in the connective tissues, specifically aponeuroses, fascia and tendons, and the muscles are only secondarily affected. (Rosenstirn[40] suggested "fibrocellulitis.") It is not entirely improper to refer to it as fibrositis since the lesions may appear to be quite inflammatory during early stages. However, "fibrodysplasia," the term suggested by Bauer and Bode,[2] impresses me (as it has Falls[9]) as most valid. "FOP" is the abbreviation which will be used in this discussion.

In a review of the subject to which little has since been added, Rosenstirn[40] in 1918 abstracted 119 cases and added his own. The first case may have been described in Guy Patin in 1692. Extraordinarily clear descriptions of the end stages of the disease were provided in the *Philosophical Transactions of the Royal Society of London* in the first half of the eighteenth century by John Freke and others. Abernethy, Caesar Hawkins, Jonathan Hutchinson,[28] Volkmann, Kronecker, Virchow, Stephen Paget, Rolleston,[39] Garrod, F. Parkes Weber, Eugene L. Opie, and many others added cases. Since Rosenstirn, other reviews have appeared.[29,34]

Helferich[20] is generally credited with having first described (in 1879) the important association of microdactyly with FOP. The distinctive type of deformity seen in these cases (monophalangy of the great toe) had been described as an isolated anomaly by Fränkel[10] in 1871.

In 1901 Rolleston[39] expressed the opinion that the disease is a defect of the mesoblast. This was probably one of the earliest statements of this idea. It has been stated by many others since that time. For example, Hirsch and Low-Beer[21] called it an "exceedingly unusual anomaly of the mesenchyme."

THE CLINICAL MANIFESTATIONS

The onset of the process in the fascia and tendons may be in fetal life[23,30,40] or rarely not until after the age of 20 years.[11,21] Usually, however, evidences of the disorder appear in the early years of life, before the age of 10 years.

Typically, localized swellings appear first in the region of the neck and back and later the limbs. They are sometimes painful. These lumps come and go in a matter of days. Sometimes injury appears to be involved in their inception. The lumps may or may not be attached to deep fascia. Sometimes the tumors are cystic and appear to contain blood. Discharge may occur. At times fever is associated with the development and/or absorption of the tumor. In fact, acute rheumatic fever may be simulated.[41] As the disorder progresses, wryneck deformity may develop. The masseter may also be affected, but the tongue, heart, larynx, diaphragm, and sphincters enjoy immunity from the process. The dorsal aspect of the trunk and the proximal (but usually only the proximal) portions of the extremities may be affected. The plantar and palmar fascia may be involved. At the attachments of fibrous structures to bones it is not uncommon for exostoses to develop, for instance, in the occipital area of the skull or as an anterior calcaneal spur.

Eventually, columns and plates (Fig. 2,*B*-2,*D*) of bone replace the tendons, fasciae and ligaments. The spine may become completely rigid and the victims converted into columns like Lot's wife at Sodom. Koontz'[25] patient "was completely unable to sit down . . . she either had to lie down or stand up. She had enough motion in one of her knee joints so that she could walk with a very halting, mincing step. She was of slight build, weighing very little, and it was simple to carry this plank-like girl around."[26] Fairbank[8] presents drawings of skeletons showing extensive changes. Often a ridge of bone on the back appears like a handle by which the patient can literally be lifted.[43]

The skin is usually exempt as are the muscles of abdominal wall, perineum, and eye. The heart is not affected. Remissions and exacerbations are characteristic of the disease. Hernias may occur with increased frequency.[40]

In spite of marked involvement, patients have survived to fairly advanced years, e.g., 61 years in case 73 described by Fairbank.[8] The patient who was 17½ years old when studied by Koontz[25] is still living and reasonably well, although severely disabled, at the age of 47 years.[26]

Obviously, microdactyly can be a valuable diagnostic sign in the earlier stages of the process of ossification or before calcification has appeared. The

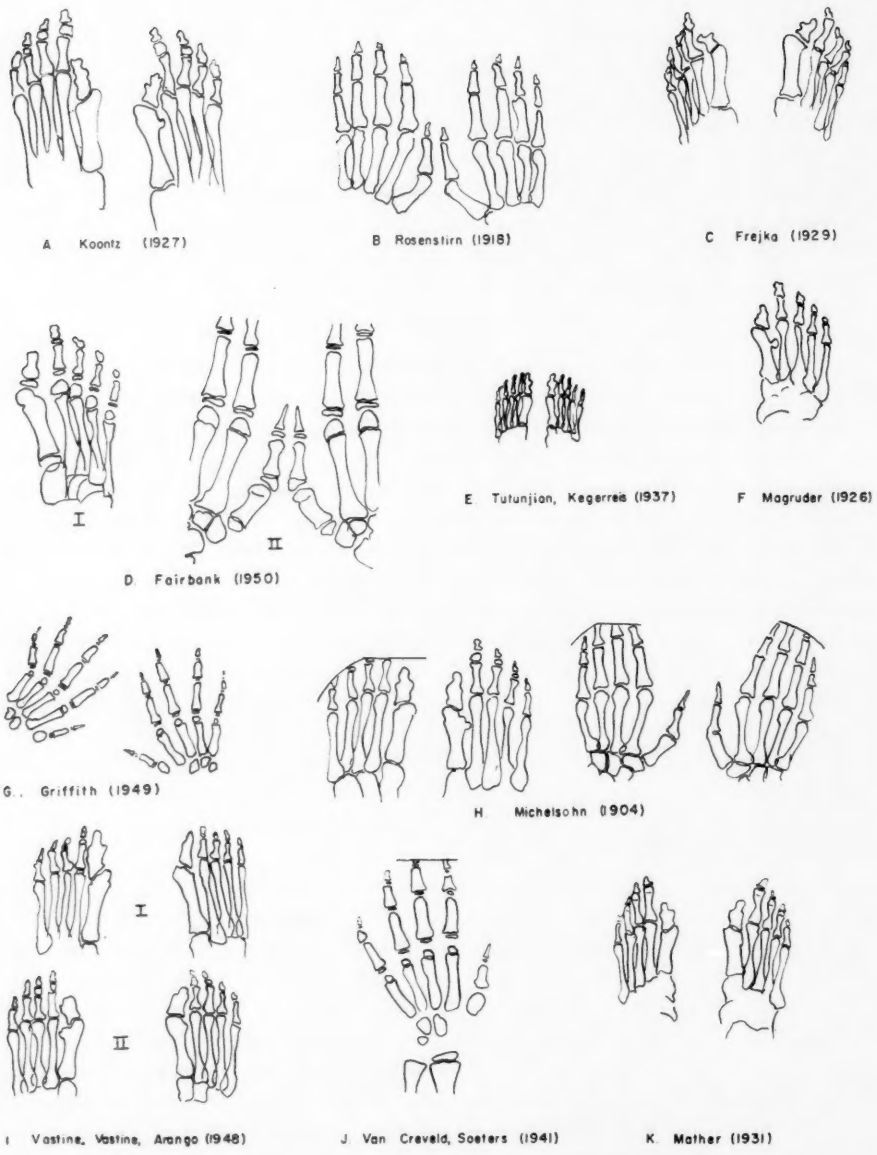

Fig. 1.—Tracings of x-rays of hands and feet in selected reported cases (These are not reproduced to the same scale.) *A*, Koontz[25]: Hands little affected. In feet, monophalangic first digit and biphalangic fifth digit. On the right the fourth toe is also biphalangic. There is an exostosis on the right great toe and bone bridge between metatarsals on the left. *B*, Rosenstirn[40]: The short, pointed terminal phalanx of the thumb is typical. The first metacarpal on the left is abnormal in shape. (Frequently the first metacarpal and metatarsal has a disorganized tuberular pattern.) The terminal phalanges of the other digits, especially the second and third, also short and pointed. *C*, Frejka[11]: The fingers were not commented on. The first toe is monophalangic and the others biphalangic at the most. Typical hallux valgus is present. *D*, Fairbank[7]: I, Aged 7 years. First metatarsal appears to have been lengthened by fusion with the proximal phalanx. The other toes are all biphalangeal. II, Aged 10 years. The characteristic short, pointed terminal phalanx is seen. There was also microdactyly of the great toes. *E*, Tutunjian and Kegerreis[43]: No comment on the state of the hands.

(*continued on opposite page*)

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great toe (Fig. 1) is affected in the great majority of cases, the thumb less frequently (in less than half of cases), and at times other digits. Hallux valgus frequently results and is often what impresses the observer rather than shortening of the digit (Fig. 2,*A*). Fairbank[8] states that all the fingers were shortened in two cases. The shortening is the result of change in the phalangeal bones, rarely in the metatarsals. The proximal phalanx may be completely suppressed. A synostosis of the phalanges of the great toe is perhaps the most typical change. Rosenstirn[40] believed that microdactyly was present in all true cases of FOP. Furthermore, the classical review of digital anomalies by Pol[37] indicates that the changes in FOP (see Fig. 1) are in all likelihood unique to this condition and, for practical purposes, absolutely pathognomonic. Clinodactyly, radial curvature of the fifth finger, may occur in these cases.

The only other skeletal change which has been seen at all frequently is an abnormally broad neck of the femora[16,45a] (Fig. 2,*B*).

Occasionally there is tendency to bruise with negligible trauma.[16] No defect of coagulation is demonstrable in these instances, however.

REVIEW OF CASES

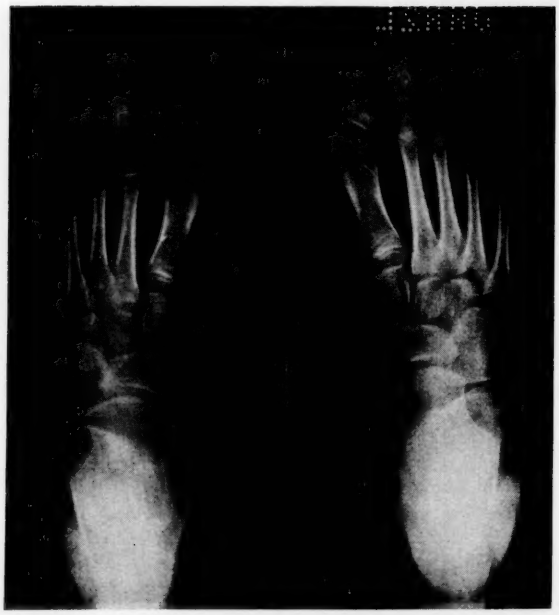
To my knowledge only six cases of FOP have been seen in this hospital during the past thirty years.* All patients are still living. One was reported by Koontz.[25] Two were briefly referred to by Geschichter and Mazeritz.[14] In none of these six families has another case of FOP been known. All the patients have deformity of the toes and/or fingers. In at least two instances (Cases 1 and 2) digital deformity was also present in other members of the family. One patient (Case 5) did not notice any abnormality until the age of 25 years, when lumps appeared above one knee. In another patient (Case 3) torticollis was noted at 1 month of age and advanced FOP was present when he was seen at the age of 16 months. Biopsies have been made in at least the last five patients. Although there is generally said to be a predominance of males affected, three of the six are female. Alkaline phosphatase determinations are available in three patients and are not in excess of values anticipated for the patient's age.

*Barker's[1] case was probably calcinosis universalis and not FOP.

(*Legend continued from opposite page.*)

It is interesting to note that monophalangic first toe can be present without microdactyly or hallux valgus. *F*, Magruder[29]: Typical monophalangy of first toe and biphalangy of others. Note exostosis like that in Koontz's patient. *G*, Griffith[16]: Typically short, pointed terminal phalanx of thumbs and of other fingers. Clinically the fifth fingers were curved (clinodactylous). The great toes were monophalangic. *H*, Michelsohn[33]: First toes monophalangic; fifth toes biphalangic. Typical thumbs. *I*, Vastine, Vastine, and Arango[45a]: Identical twins. Monophalangy of first toes. Biphalangy of fourth and fifth toes. *J*, van Creveld and Soeters[44]: Aged 5 years. Typical thumb. *K*, Mather[32]: Monophalangic first toe. Biphalangic fifth toe.

It is noteworthy that in the feet of many of the patients in the illustrated cases of FOP, sesamoid bones have been conspicuous by their absence. In their place, projections like exostoses occur, particularly at the distal end of the first metatarsal. It is likely that these "exostoses" are synostoses of sesamoid bones with the metatarsal.



A.

B.

Fig. 2.—X-ray studies in Case 2 of FOP (see text). As demonstrated in *A*, there was distortion of the contour of the distal tip of the first metatarsal and the proximal phalanges resulting in the hallux valgus deformity seen clinically. It is of note that in this case a normal number of phalangeal bones are present in all the toes. This is, as will be seen from inspection of Fig. 2, the expection; as a rule, monophalangy of the great toes is at least present. It will be interesting to see if synostosis occurs in the future as was observed to occur in Michelsohn's patient.[33] The hands were normal. As demonstrated in *B*, the neck of the right femur is slightly widened and blunted; immediately adjacent to the epiphyseal line the left femur is normal. Anomalous bone is seen on each side of the lower lumbar spine, especially the left. The ossification in the axillary areas (*C*) has the appearance of cortical bone. In places, it resembled the ribs in contour. At least one false joint was identified. In the lateral view of the lumbar spine (*D*) plates of bone are clearly demonstrated on the back.

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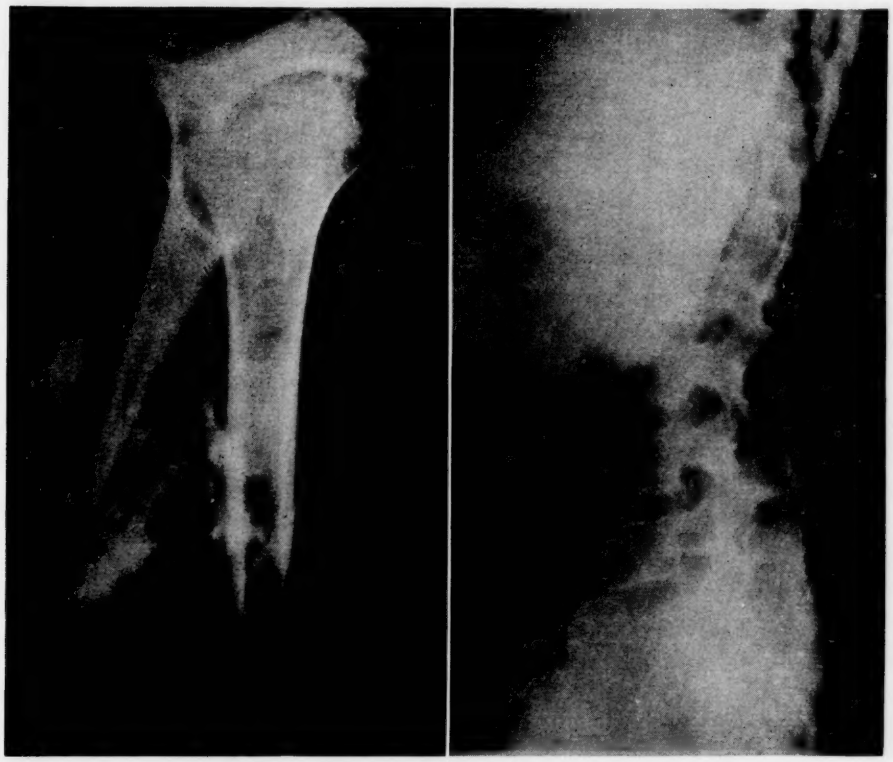
Abstracts of these six cases follow:

CASE 1.—The case of N.J., born in 1908, was reported by Koontz[25] in 1927, with excellent illustrations of the gross appearance and radiologic changes including those of the thumbs and great toes. The maternal grandfather and his two brothers developed late in life what apparently were Dupuytren contractures. A cousin on the maternal side apparently had a deformity of the toes similar to the patient's. The patient's first symptom was stiffness at the age of 9 years. Menstruation never occurred. Both great toes and thumbs were short and malformed. Concentrations of calcium and phosphorus in the blood were normal.



C. *D.*

Fig. 2,*C* and *D*. *(For legend see opposite page.)*

CASE 2.—B.W. (A85874), a 7½-year-old white girl, has a normal brother and sister. The father had stunting of the great toes similar to the patient's but no other instance of FOP is known in the family. At 10 months, when the patient began to sit up, the head leaned to the left. At the age of 6½ years, she developed an exostosis on the right knee after trauma. However, she remained apparently otherwise well until the age of about 7 years, when she began to complain of pain in the left side of the neck, and firmness and tenderness was discovered there. Thereafter, swelling and induration developed on the back, abdomen, and shoulder. There was marked limitation of motion of the neck, arms, and spine, and the head was held to the left. Dermatomyositis was the initial diagnosis. See Fig. 2 for x-ray studies of this patient.

CASE 3.—R.W. (A62462) was found at birth to have hallux valgus and short thumbs. At 1 month the head was noted to be bent to the left and there was a firm mass in the sternomastoid muscle. Thereafter asymmetry of the face developed. Lumps appeared in many areas over the back and scalp. These masses never appeared inflamed. There were, however, frequent bouts of unexplained fever. Examination revealed atrophy of the left side of the face. The

sternomastoid muscle on the left was converted into a stony hard mass. The ligamentum nuchae was similarly affected. Extensive involvement about the scapulae (which were attached to the ribs) and the trapezius muscles formed a yoke on the back.

CASE 4.—V.W. (U52691) has seven siblings, but none has either microdactyly or FOP. She was presumably well until the age of 6 years, when she fell from a swing striking her back. Swelling and discoloration resulted. X-rays at that time revealed "a spider's web on the spine." Thereafter, there was steadily progressive increase in stiffness and limitation of motion of joints. The thumbs and toes had always been small. It is of note that the facial muscles were involved in this case. By the age of 25 years the jaws became locked and the upper teeth had to be removed to permit alimentation. (See Fig. 3 for drawings of this patient.)

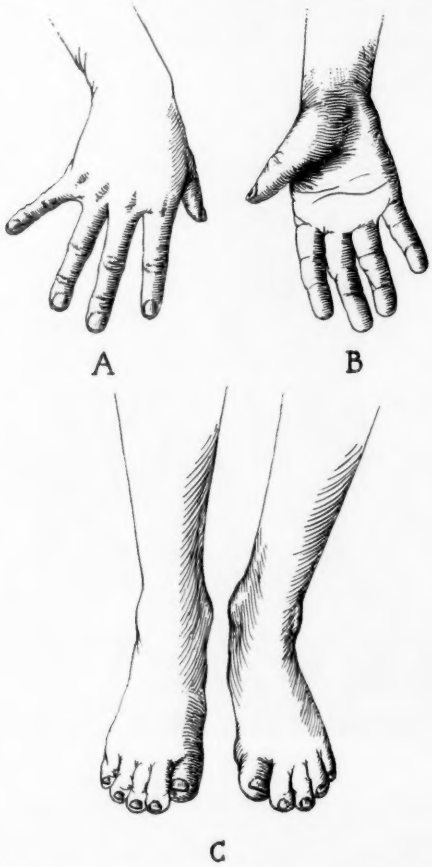


Fig. 3.—Drawings of the hands and feet of Patient 4 of the FOP series (see text). Microdactyly of the thumbs and toes is strikingly demonstrated.

CASE 5.—F.K. (U52689) was well until the age of 25 years, when he developed a "bump" above one knee following trauma. During the following year there were several episodes of soreness and swelling in the left side of the neck with difficulty in swallowing. There are six siblings. No other members of the family had microdactyly or ossification. The patient's thumbs were small with fusion of the interphalangeal and metacarpophalangeal joints. All the terminal phalangeal joints of the second and fourth fingers were fused. Hearing was impaired bilaterally. As long as the patient could remember, he had had restriction of motion of the head, mandible, both shoulders, right elbow, both thumbs, both hips, left knee, left ankle, and toes of the left foot. Supposedly, poliomyelitis affecting mainly the left leg had occurred at 5 years of age, but suspicion is cast on the diagnosis by later developments. (See Fig. 4 for drawings of this patient.)

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CASE 6.—M.W. (422628) was seen at the age of 14 years and a diagnosis of calcinosis of the muscles of both hips was rendered. However, in retrospect there can be no question but that FOP was actually present. The boy had always been stiff and following a blow on the back at the age of 5 years a lump on the left scapula was noted. The mass was biopsied and called sarcoma. The boy was given only 3 months to live; he is still alive, although disabled, at the age of 23 years. Other lumps appeared and flexion contracture of the hips and right knee gradually developed. The left great toe was short and deformed.

INCIDENCE AND INHERITANCE

In 1918 Rosenstirn,[40] in reviewing this disorder, could find 119 cases in the literature. In later reviews[30,34] other cases have been added. The disease is appreciably more frequent in males, in a ratio of 4:1 according to some,[41] but 3:2 by the statement of others. In Rosenstirn's collection of cases, 56 per cent were male (68 male and 54 female).

Sympson[42] reported microdactyly in father and son with FOP in the son. Drago[6] reported the same situation in a mother and son. Koontz[25] described "contractures of two fingers" in four relatives of the patient. The anomaly apparently developed later in life, however, and may have been Dupuytren's contracture. Burton-Fanning and Vaughan[5] described FOP (the full syndrome) in both father and son. Gaster[13] observed the disorder including phalangeal deformity in five male members of three generations, three brothers, the father, and paternal grandfather. Vastine, Vastine, and Arango[45b] saw it in identical twins. It may be that this disease trait is dominant with a particularly wide range of expressivity.

PATHOLOGY

The early histologic changes are not known. Obviously it is these which are of most significance in reference to the basic abnormality. It is clear[17] that the skeletal muscle is fundamentally normal. Geschichter and Maseritz[14] picture cartilage and also "young osteoid tissue surrounded by osteoblasts." The surgical pathologist may find it difficult to distinguish FOP from osteogenic sarcoma. In the case described by Paul[36] both were thought to have been present.

THE BASIC DEFECT

That the fundamental disorder resides in connective tissue seems indisputable. Isolated bone tissue may be found in the skin[40] well removed from muscles. No aberration of calcium metabolism has been demonstrated. Because of the similarities of behavior to the calcification and ossification which occurs after traumatic and other injury which involves necrosis of tissue, one suspects that this is fundamentally a dystrophy of connective tissue with secondary calcification. What is seemingly the identical disorder, even with microdactyly, has been described in a setter dog by Rosenstirn,[40] and spontaneous ectopic ossification is also said to occur in the horse. Rosenstirn believed that the fundamental defect resides in the small blood vessel and that the initial lesion is a hemorrhage which is followed by organization and ossification.

The observations of Wilkins, Reagan, and Carpenter[47] are important and point the way to an area for possibly productive investigation by other techniques such as tissue culture of fibroblasts from these patients. Specifically they found a very high level of alkaline phosphatase activity in the areas of heterotopic cartilage and bone formation. The activity was, in fact, higher than in normal rib.

An enigmatic feature of this syndrome has been the association of an anomaly of the conventional congenital type, microdactyly, with the other cardinal component, ectopic ossification, which behaves more like an hereditary weakness of some element of connective tissue. Previously, in discussing the explanation for the association of congenital anomalies of conventional types with hereditary disorders which behave more like abiotrophies, it was proposed that the presence of a basic tissue defect results in an abnormal environment for embryologic development so that specific congenital defects occur predictably with increased incidence. Such may be the case with the microdactyly of FOP. Certainly, a disorder of normally ossified tissues is not too farfetched an association. However, a more straightforward explanation is possible. There is an intriguing set of observations reported by Michelsohn[33] suggesting that in connection with the abnormality of growth of the first digits in FOP there is no sharp distinction between antenatal and postnatal developments. The patient in question was a 17-year-old girl when seen. In the first months of life the mother noted pronounced shortening and stiffening of the great toes with no morphologic or functional abnormality of the thumbs. At the age of 7 years when the changes in the muscles were beginning, the thumbs became painfully swollen and later stiff, then ankylosed. By definition the change in the great toes was synostosis and that in the thumbs ankylosis. However, it may be that the same basic process was operating in both instances.

The malformation of the digits appears to occur in the fairly regular manner of a Mendelian autosomal dominant trait; ossification occurs in much more spotty fashion. The factors determining whether ossification will occur in a given case of microdactyly are entirely obscure. Rosenstirn[40] reported that both FOP and microdactyly occurred in a dog. It is a pity that breeding and other experiments were not undertaken on this valuable animal.

OTHER CONSIDERATIONS

In the differential diagnosis, calcinosis universalis, dermatomyositis, Weber-Christian's disease and other conditions must come in for consideration. The picture suggests torticollis in the early stages.[30] Calcinosis universalis is probably basically a "collagen vascular" disease with secondary calcification.[46] It is certainly not an heritable disorder. The patient described by Barker,[1] a Negro male who was for many months on the wards of the Johns Hopkins Hospital, probably had calcinosis universalis and not FOP. Actually there must be very few descriptions of FOP in Negroes.

Beryllium has been used in the treatment of FOP.[43] Since beryllium suppresses alkaline phosphatase activity,[18,24] there might be some rationale for this therapy. This effect of beryllium was, however, unknown in 1937 when it was

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used; furthermore, its effect was, at the most, doubtful. Adrenocortical hormones were used in Case 2 and in patients reported in the literature.[28,38] Benefit has been, at the most, dubious. Somewhat encouraging results in an early and active case were described by Riley and Christie,[38] but no benefit was noted in an old, probably static case. X-ray therapy may aggravate the condition. The reader is referred elsewhere (e.g., ref. 38) for reviews of the other forms of therapy which have been employed without any particular success.

SUMMARY

The cardinal manifestations of fibrodysplasia ossificans progressiva are microdactyly and progressive ossification of fascia, aponeuneuroses, and other fibrous structures related to muscles. Microdactyly is always most striking in the thumb and great toes. It probably represents fundamentally the same disorder occurring usually, although not exclusively, during antenatal development. There is usually a synostosis with resulting monophalangic great toe.

This disorder is probably inherited as a Mendelian dominant with irregular penetrance.

C. Osteopoikilosis (Osteo-dermato-poikilosis)

Osteopoikilosis, like osteopetrosis, was first described in a definitive manner (earlier references[71] can be found) by the German radiologist, H. Albers-Schönberg (1915).[48] It is sometimes referred to as "spotted bones," an appropriate designation as is seen from Fig. 5. "Osteopoikilosis" (variations "osteopoecilia," "osteopecilia," "osteopoicilosis," "osteopoikilie") is derived from Greek words meaning "mottled bones." The bone lesion is also referred to as "osteitis condensans generalisata" or "osteosclerosis disseminata." The skin lesions were first described in 1928 by A. Buschke and Helen Ollendorff[52] (later Curth[57]) as "dermatofibrosis lenticularis disseminata." Osteo-dermato-poikilosis might be a satisfactory designation for the entire syndrome.

Neither the osseous nor the cutaneous lesions are of any clinical significance whatever. They are usually discovered incidentally since the bone lesions are asymptomatic and the skin lesions inconspicuous. One reason why the clinician should be familiar with this condition is that he may avoid confusing the condition for osteoblastic metastases to the skeleton.[68]

The bone lesions are circumscribed, round areas of increased bone density, usually less than 1 cm. in diameter, situated particularly at the ends of the bones of the extremities (but not necessarily in the epiphyses) and in the small bones of the feet and wrists (Fig. 4). The lesions may or may not be bilaterally symmetrical. At times the lesions are linear (striate) in distribution.[77] For example, Voorhoeve[75] found vertical striae parallel to the long axis of the bones and as a fan in the wings of the ilia, but no spots, in two children whose father had typical spots and no striae. See Fig. 6 for a demonstration of the distribution of lesions. The skull has been spared in most cases. Bistolfi[49] described involvement of the occipital bone. All three cases of Funstein and Kotschiew[59] had skull involvement and indeed the calvarial lesions dominated the picture in Erbsen's[58] case. In the case of Martinčić[63] unusual involvement of the lumbar spine was present.

As was nicely demonstrated by Funstein and Kotschiew[59] the islands tend, in pronounced cases, to be oriented along the "traction and pressure lines,"[63] especially at points of crossing of these lines.

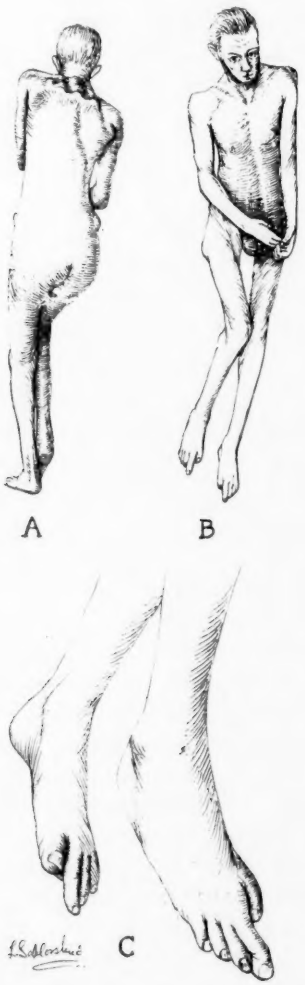

Fig. 4.—Drawings of Patient 5 of the FOP series (see text). The ridges of bone on the back and the fixedly awkward posture are highly characteristic. Striking microdactyly is also present.

The skin lesions, always inconspicuous, are most often located on the posterior aspect of the thighs and buttocks, occasionally on the arms and trunk but never on the face. Their location bears no constant relation to that of the bone lesions, although it is noteworthy that the head is usually affected neither by skin nor by bone lesions. They are closely situated, slightly elevated, whitish-yellow in color, and usually oblong or oval in outline. Like the bone lesions they have been described as occurring in longitudinal streaks. They are usually

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about the size of a lentil or pea, from which the name of the lesions is in part derived. Most of the cases of bone lesions that have been subjected to careful inspection have been found to show skin lesions as well. Busch[51] described skin changes in 6 patients, Buschke and Ollendorff[52] in 1, and Šváb[72] and Windholz[77] in 2 each.

Information on the age of appearance and evolution of both the osseous and cutaneous changes is meager. It is clear that lesions may be present at both sites in the first years of life. Furthermore, it appears that once formed, the bone lesions remain static for many years. The longest reported follow-up, seventeen years, was in a female first observed at the age of 14.[64]

Fig. 5.—Typical osteopoikilosis discovered incidentally when radiologic studies for a wrist injury were performed (J.H.H. 644704) in a 13-year-old white boy.

Keloids may occur with increased frequency in these patients.[57] The only internal medical ramification that has even been suggested is that of fibrous nodules of the peritoneal lining discovered at laporotomy in a 13-year-old patient who complained of severe abdominal pains.[70] It can fairly be stated that this was not a "clear case," however. Grossly the nodules suggested tubercles. Scleroderma beginning at the age of 7 months was described in association with osteopoikilosis by von Bernuth.[74] However, I doubt seriously that the bone condition described and pictured was the same as that under discussion here.

In a case reported by Nichols and Shiflett[64] an obscure generalized skeletal disease was present in addition to osteopoikilosis; the authors thought there was no connection. In general, one seems justified in considering this situation as incapable of producing symptoms and as prognostically insignificant.

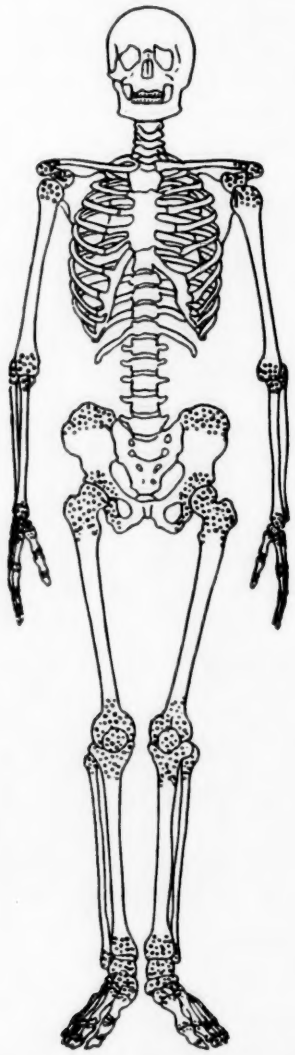

Fig. 6.—Typical location of bone lesions in osteopoikilosis.[19]

The bone lesions were examined histologically by Schmorl[69] in an 18-year-old boy who died of seemingly unrelated cause. He found that each "island" is a clump of osseous trabeculae which are thicker at the periphery than at the center. The trabeculae at the center form a complex network with ordinary

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marrow in the space between. The skin lesions consist of collagenous fibrosis with preservation of the elastic fiber elements.[51,52]

From the point of view of inheritance this disorder behaves as a Mendelian autosomal dominant. Busch[51] found 14 cases in 3 generations of one family and the condition probably extended further back in the ancestry since there were three affected siblings in the first generation studied. Hinson[60] studied it in two generations. In x-rays of the entire skeleton Bloom[50] found only a single spot in the sister of a patient with widespread involvement. Wilcox[76] saw the bone condition in father and daughter; Voorhoeve[75] in father, son, and daughter. Risseeuw[67] saw the disorder in a man, six of his children, and a grandson.

The basic defect appears to be a spotty hyperplasia of collagen in the corium and bone matrix. This is, however, little more than a restatement of the histologic findings. What is basically involved in this defect, why the peculiar spotty distribution, is obscure. Voorhoeve[75] thought the bone lesions arose in cartilage. He based this theory on the fact that in two children he observed striate lesions extending a variable distance into the diaphysis from the epiphyseal line. The relative immunity of the skull and clavicle ("membranous bones") may be supporting evidence for enchondral origin.

Copeman[54] saw osteopoikilosis in association with rheumatoid arthritis.

Traub[73] has described mottling of the epiphyses, superfically resembling the hereditary condition, in cases of pituitary gigantism, and a vaguely similar picture is associated with cretinism.[66]

In a paper entitled "Follicular atrophoderma and pseudopelade associated with chondrodystrophia calcificans congenita," Curth[56] has written about an interesting familial and almost certainly hereditary disorder involving bone and skin. As indicated in her references to the literature, others have reported cases. In the case of the skin involvement it may be connective tissue that is primarily affected and not the epidermis. However, studies to date leave the nature of the basic defect in question. It is certainly distinct from osteo-dermatopoikilosis. There is probably no fundamental kinship between so-called "strippled epiphyses" (chondrodystrophia calcificans congenita[55]) and osteopoikilosis.

D. Léri's Pleonosteosis

In 1921 André Léri,[82] Parisian orthopedist, described a previously unrecognized condition in a 35-year-old man and his children by a second wife, a daughter aged 4 years and a son aged 3 weeks. The child by his first wife was normal. The disorder was not present at birth and became evident sooner or later in extrauterine life. The father was only 62 inches tall, and had short, broad hands and feet with thickened palmar pads and accentuated creases, and limitation of motion in the wrists, elbows, hips, and knees. The toes, and presumably the thumbs as well, were broad and stiff. Fairly numerous cases have since been described in the French literature,[81,83,86,87,89,90] including one report from Russia,[79] some in the German literature (see ref. 85 for list of German reports), and there have been reports in journals of Brazil and Argentina (see ref. 91) but there appears to be only one article in British journals[91] and none at all in the periodical American medical literature.

The term "pleonosteosis" suggested by Léri was based on his impression, probably inaccurate, that the basic abnormality is one of excessive ossification.

The clinical characteristics of Léri's pleonosteosis are broadening and deformity of the thumbs and great toes, flexion contractures of the interphalangeal joints, and limitation of motion in other joints, including even those of the spine. A form of "hammertoe" may develop. Mongoloid facies have been described[91] but are by no means an invariable feature (see case 1 of ref. 91). Furthermore, in the majority of cases of mongoloid features, the patients are normally intelligent, e.g., Watson-Jones'[91] patient 2 who was a university graduate. However, there are at least two reports of impairment of the intellect.[86,90]

There is usually semifixed internal rotation of the upper limbs and external rotation of the lower limbs. In general the limbs are short. The joints of the hands in particular may appear to be swollen. The hands are short, square, and thick. Changes in the lower extremities seem to be less striking, but this may be a function of the fact that less intricate movements are required of the feet and ankles.

A complication of the fibrous hyperplasia in the hands and feet can be nerve compression: carpal tunnel syndrome involving the median nerves and Morton's metatarsalgia from involvement of the digital nerves of the feet.

Watson-Jones[91] described the dense fibrous tissue removed from the wrist and consisting essentially of a highly hyperplastic anterior carpal ligament. The specimen consisted of greatly increased, dense collagenous tissue which in portions was actually fibrocartilage. Elastic fibers were conspicuous in their absence. Mucinous material was present and, in tissue removed from the foot, numerous "tissue mast cells" were described.

The fundamental abnormality was thought by Léri to be one of excessive and perhaps precocious ossification of the epiphyses. It seemed more likely to Watson-Jones[91] that the joint deformities are due to capsular contractures, that in general the abnormality resides in the fibrous tissues, and that the "thickening of the bones may be due to periosteal traction at their metaphyseal attachments."

All evidence suggests that pleonosteosis is inherited as a Mendelian autosomal dominant trait.

Although uncommon, Léri's pleonosteosis almost certainly occurs more frequently than the absence of reports in American journals would suggest. In their monograph *Human Heredity*, Neel and Schull[86] describe a 34-year-old woman with progressive loss of joint mobility and moderately severe contractures beginning in adolescence. Movements of the hands in particular were awkward and clumsy. The mother, aged 58 years, was affected and by this time of life was unable to perform most fine movements of the hands and the rest of the body. A brother of the proposita and a half-brother of her mother were also affected. A feature of all affected persons was a broad thumb. The proposita sought information on whether her two sons would be affected. Since one of them already displayed broad thumbs, the inquirer was advised that a vocation requiring manual dexterity would be inadvisable.

The nosography of this disorder is far from fully established. Cocchi[78] includes this condition in the group of "polytopic enchondral dysostoses" in which

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he also includes the Morquio syndrome and the Hurler syndrome. In a detailed clinicopathologic study based on two brothers, Materna[85] described what he called Léri's pleonosteosis, which differs radically from the condition in the four patients reported by Watson-Jones.[91] There was no mention of limitation of joint mobility. The entire skeleton revealed extensive changes with "innumerable microfractures," fish vertebrae, a wedge vertebra, and coarsening and widening of the tubular bone, among other changes. The father was thought to have the same disorder as his two sons. One of the sons died at the age of 42 years of heart failure; no autopsy was performed. In the other, heart disease believed to be rheumatic was discovered at autopsy. This brother had had repair of bilateral inguinal hernias at the age of 14 months.

In the differential diagnosis, the Hurler syndrome and arthritis, either rheumatoid or degenerative, come in for consideration. One would be suspicious that the case thought by Rocher and Pesme[87] to be one of pleonosteosis with corneal opacification was, in fact, one of the Hurler syndrome. Sometimes thoracic outlet syndrome (compression of components of the cervical plexus) is suspected.[91]

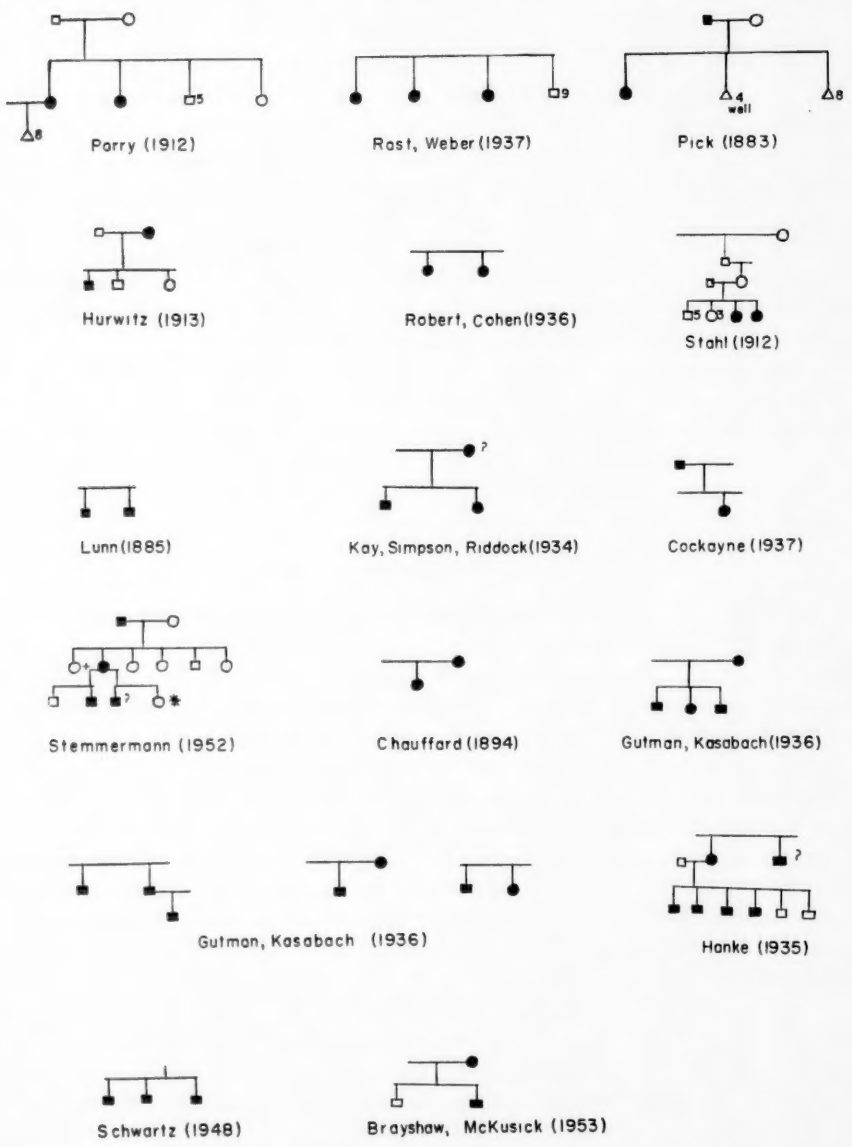
E. Paget's Disease of Bone

Is Paget's disease of bone a generalized disorder of connective tissue? The evidence that Paget's disease of bone can legitimately be considered an heritable abiotrophy, probably of the collagen matrix of bone, can be summarized in the way indicated below. None of the pieces of evidence is by itself conclusive, but taken together they make a rather convincing argument.

1. The hereditary nature of the process appears to be established. However, it is worth while examining the evidence for this, since a recent review,[134] which is otherwise comprehensive, makes no mention of the genetic factor in discussing etiology. In 1889 Paget[129] himself wrote: "I have tried in vain to trace any hereditary tendency to the disease. I have not found it twice in the same family." However, the observations of familial aggregation reported from even before that time (beginning with Pick[131] in 1883) are fairly numerous (see Fig. 7).

In 1946 Koller[117] could find in the literature 28 families in which more than one case was described. Since then other reports[93,94,100,113,115,122,127,137,143] of familial aggregation have appeared. Stemmermann[143] identified it in members of three successive generations. It appears to have occurred in four generations of a Jewish family known to me, and also in two other kinships as indicated in Fig. 7. Aschner, Hurst, and Roizin[93] described it in monozygous twin brothers and claimed that by 1952 a total of 57 families with multiple cases had been described. Martin[121] and others (see Fig. 7) also described the disease in both of identical twins.

When one undertakes to study the heredity of a condition such as Paget's disease, one encounters several difficulties. In the first place, the disease has some of the earmarks of an abiotrophy. That it is an abiotrophy remains, of course, to be established. At any rate the disease usually has its onset late in life, by which time the parents are likely to have died, the siblings may be widely scattered geographically, and the children will probably not yet be old enough



A.

Fig. 7.—*A* and *B*, Thirty-five pedigrees from the literature and two from the unpublished experience of Brayshaw and McKusick, showing familial aggregation of Paget's disease. Moehlig[122] and Ashley-Montagu[54] and probably others reported Jewish pedigrees. Concordance in identical twins was reported by Koller,[117] by Mozer,[126] and by Dickson, Camp, and Ghormley.[102] In the last instance there was a striking similarity of distribution in the twins, both having, for example, tibial involvement. In the twins observed by Mozer[126] onset of the clinically evident abnormalities occurred at the age of 48 years in both. In Irvine's[113] pedigree the affected male died of a malignant osteoclastoma of the jaw and both daughters had the onset of Paget's disease of the skull and jaw at the age of 18 years. In the pedigree of Brayshaw and McKusick in Fig. 1,*B*, the first individual in the second generation, a female (A.H. 511948), had so-called osteitis pubis and changes in the skull compatible with Paget's disease. The alkaline phosphatase, however, was always normal. The other two affected individuals (C.T. 502845; W.T. 620032) had Paget's disease in entirely typical form. These patients were discovered on study of the records of the hospital; if a more detailed study of the family were made, other members would probably be found to be affected.

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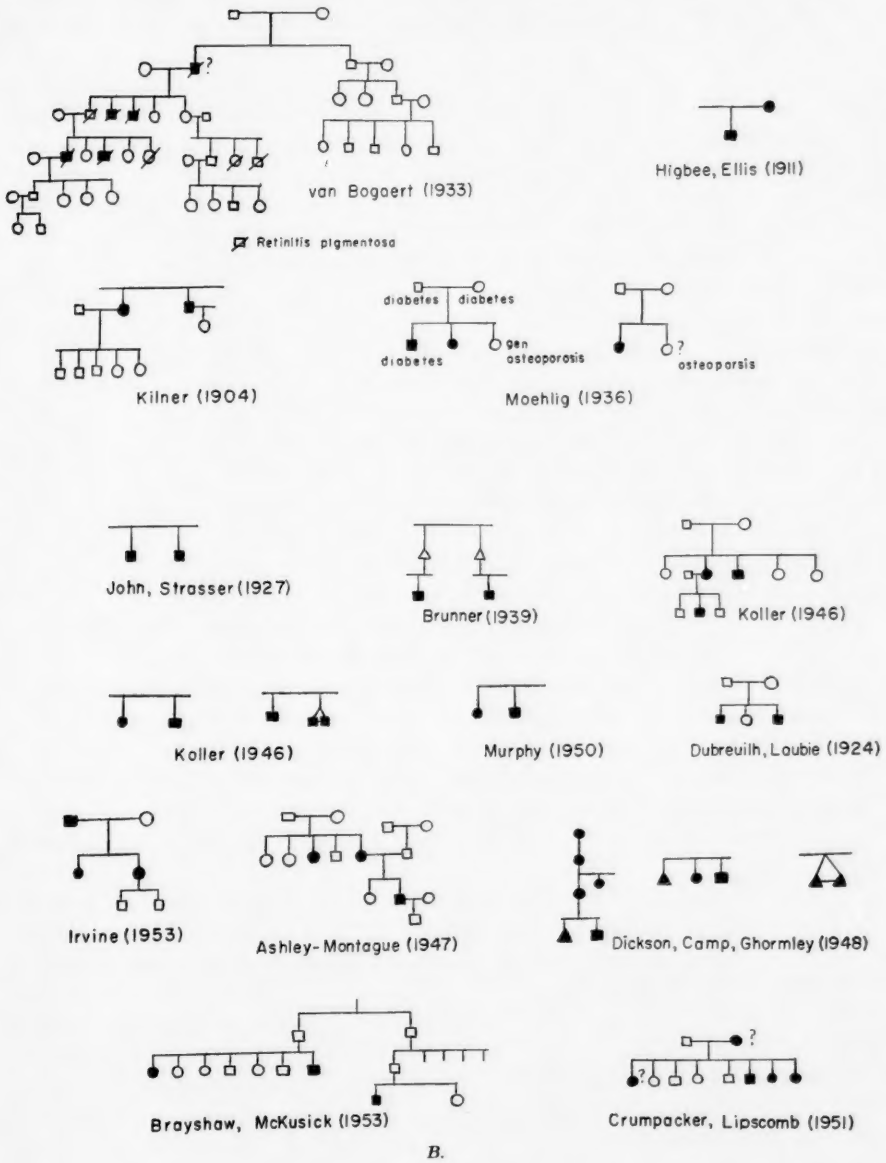
to have developed the disease. In the second place, Paget's disease is often subtle in its manifestations. A very high proportion of affected persons are asymptomatic and the change in bone is discovered only incidentally on radiologic examination made for unrelated purposes or possibly in search for an explanation of an otherwise obscure elevation of serum alkaline phosphatase activity. In the course of the detailed study of 7,941 individuals over 61 years of age, 85



B.

Fig. 7,B. *(For legend see opposite page.)*

cases of Paget's disease were found, but of these cases only three had complaints referable to the disorder of bone.[124] In connection with the last difficulty it may be that a study of families, using alkaline phosphatase determinations as a screening procedure, would be productive. The first type of difficulty—the age factor—would not, to be sure, be circumvented.

In general, the data accumulated are consistent with the view that the trait for Paget's disease is controlled by a simple autosomal Mendelian-dominant gene. However, Ashley-Montagu[94] suggested that it is inherited as a sex-linked recessive.

Considering how frequently Paget's disease occurs in at least mild form (3 per cent of all persons over 40 years of age, according to Schmorl[136]), one might say that it would be extraordinary if 30 or 40 families with more than one case could *not* be discovered. Along the same line it may be noted that Sabatini[135] found Paget's disease in two married couples in which the marital partners were unrelated. Actually I believe there is a significant familial aggregation of cases. Particularly in the pedigrees with more than two cases is the evidence convincing. The incidence of Paget's disease in the general population is roughly 0.013 per cent.[117] It can be estimated that the chance of two or more cases occurring in the same family by random distribution alone is very slight indeed.

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2. Angioid streaks of the retina are associated with only two conditions with any regularity. These are pseudoxanthoma elasticum and Paget's disease of bone.[125,145] Although there are statements in various reviews that the changes of pseudoxanthoma elasticum in the skin and of Paget's disease in the bones have been observed in the same patient, I have found no such case in my own experience and there seems to be only one definitive description of the association in the literature.[150] There are other reasons for believing there is no fundamental relationship between Paget's disease and pseudoxanthoma elasticum: the first is usually inherited as a Mendelian dominant, the second as a Mendelian recessive; the first occurs more frequently in men, the second in women. (Paget's disease seems to occur more commonly in men but in more severe form in women.)

Although clearly Paget's disease and pseudoxanthoma elasticum are basically distinct entities, the fact that angioid streaks, which are an integral part of a definite disorder of connective tissue (PXE), occur also in Paget's disease suggests that Paget's disease may likewise be a disorder of connective tissue with abnormalities much more widespread than the bone lesions alone would suggest.

Also in Paget's disease, there occur other ocular abnormalities such as corneal degeneration,[147] cataract,[118] and choroiditis[98] independent of angioid streaks, which raise further the question of whether a generalized abiotrophy of connective tissue may be present.

3. A quality of reasonableness, although not constituting proof, makes it attractive to persons familiar with bone and with the clinical behavior of Paget's disease to speculate that the disease is fundamentally an abiotrophy of the collagen matrix of bone which breaks down with the passage of years. Albright[92] presents evidence that Paget's disease is primarily a destruction or, perhaps it is permissible to say, a degeneration of bone with secondary reparative overproduction of bone.

In general, the involvement of the skeleton follows a pattern of localization consistent with the view that "wear-and-tear" is a contributing factor in the development of the lesions. Weight-bearing structures are usually involved primarily. The bones of the upper extremity, are, for example, much less often involved than those of the legs. The victims of Paget's disease in severe form are often obese. The high incidence of obesity and tallness in the families of patients with Paget's disease is emphasized by Moehlig.[122,123]

The femur[136] is one of the most commonly affected bones (over 30 per cent of cases) and the humerus one of the least (less than 5 per cent).* The most frequently affected bone is the sacrum (57 per cent of cases). The vertebrae are affected in half of cases and the incidence of involvement in descending frequency is lumbar, thoracic, and cervical spine. In brief, beginning with the sacrum there is a progressive decrease in frequency of involvement as one progresses craniad. An amazing finding[136] is that the right femur is involved by Paget's disease over twice as often as the left femur (31 per cent as against 15 per cent). Undoubtedly, people are right-legged or left-legged just as they are right-handed or left-handed. In the skull Albright and Reifenstein[92] picture an instance of predominant involvement laterally at the attachment of the masseter and temporal muscles. Involvement of other areas of the skull, often a striking feature, is more difficult to explain on a "wear-and-tear" basis. However, it must be remembered that "wear-and-tear" is only a contributing factor in the development and localization of the disorder, the primary factor being an hereditary weakness. The situation with Paget's disease may be like that of pseudoxanthoma elasticum in which "wear-and-tear" appears to be responsible for the site of principal localization of the skin changes. Schmorl[136] noted that changes tend to be most pronounced at the attachments of tendons and ligaments to bones. Kay, Simpson, and Riddock[115] made the important observation that in a brother and sister (Fig. 7A) with Paget's disease, both with unilateral involvement of the radius, the left radius was involved in the left-handed individual and the right radius in the right-handed one! This appears to be a nice demonstration of the cooperation of genetic and postnatal factors.

The significance of localized trauma preceding the onset of monostotic Paget's disease is difficult to evaluate (p. 332 of ref. 142). The reported cases may represent coincidence of phenomena.

4. Vascular disease has been thought to occur prematurely and with increased incidence in these patients.[140] This has been thought to be independent of the "high output" heart failure which may occur as a result of the vascular peculiarities which functionally resemble arteriovenous fistulae.[104,144] Medial sclerosis of the Mönckeberg's type has been thought to occur especially often in these persons. Harrison and Lennox[109] found valvular calcification in 39 per cent of their patients with Paget's disease, an incidence five times that of a control group of comparable age distribution. Vascular calcification may be related merely to the periodic hypercalcemia to which these persons are subjected. The elevation of circulating alkaline phosphatase may contribute. Extraskeletal

*The statistics listed here are derived from the classical necropsy study of Schmorl.[136]

calcification occurs commonly in these patients,[128,138,148] possibly for the reasons listed, possibly because of an abnormality of connective tissues. Urinary calculi which are frequent would seem to be explained by the high urinary excretion of calcium. Salivary calculi, which were identified in 20 of 111 cases,[134] are not so easily explained.

This fourth bit of evidence is by far the weakest of the points bearing on the possible nature of Paget's disease as an abiotrophy of the collagen matrix of bone.

Hitherto, a principal view of the pathogenesis of Paget's disease has implicated vascular changes. This view would consider as intimately related to the primary defect the increased vascularity of the bones, which may represent a significant and at times intolerable burden to the heart similar to arteriovenous fistulae,[140] is a problem in hemostasis to surgeons, for instance, the neurosurgeon performing craniotomy in instances of involvement of the skull,[101] and results in the fact that the skin overlying bones severely affected by Paget's disease may be warmer than elsewhere. In the present state of ignorance it is probably at least equally valid to suspect that Paget's disease of bone may be an abiotrophy of the collagen matrix, and that the vascular phenomena are secondary developments.

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F. Other Possible Hereditary and Generalized Disorders of Connective Tissue

Christiaens, Marchant-Alphant, and Fovet[160] have described (with clinical photographs and autopsy findings) the association of pronounced cutis laxa with bilateral and severe pulmonary emphysema. The latter was the cause of death in the 18-month-old infant. No mechanical factor to account for the emphysema was discovered. A generalized defect of elastic fibers was hypothesized and seemingly found support in the results of histologic studies. The cutis laxa present in this infant was appropriately named as indicated by the photographs which show the skin hanging, from the trunk in particular, in large loose folds. This disorder is not to be confused with either the Ehlers-Danlos syndrome or pseudoxanthoma elasticum; there is no evidence of fundamental alliance with either.

Gout and *ochronosis* (alkaptonuria) might be construed as proper constituents of this general group. Both are hereditary and, in both, connective tissues are conspicuously implicated. However, there is no good evidence that connective tissue is primarily at fault. It is true that in gout there may be a tissue factor to explain some of the peculiar observations such as the following, which suggest that hyperuricemia is not the whole story: (1) Gout does not occur regularly in association with the pronounced hyperuricemia of renal failure, leukemia, or resolving pneumonia. There are suspicions that when gout does occur in these situations the patient is by genetic background fundamentally a gouty person. (2) The solubility product of sodium biurate is not exceeded by the concentrations attained in the serum. Some other local factor must favor precipitation of urate.

In *ochronosis*, there are in the sclera, cartilage, ligaments, joint capsules, and arteries deposits of material which accumulates because of inability of the organism to metabolize phenylalanine and tyrosine beyond the stage of homogentisic acid, which is excreted in the urine.[154,168,185,192] Disabling arthritis and ankylosing spondylitis develop. Calcification of the intervertebral discs is a frequent feature in older individuals.[154] Pigmentation and calcification of the annulus fibrosis mitralis, of the heart valves and of the arteries occurs. Calcific aortic stenosis and severe arteriosclerosis may be integrally related to the metabolic defect.[185]

Osteopetrosis (marble-bones; osteosclerosis fragilis generalisata; Albers-Schönberg's* disease), although hereditary and although involving the skeletal system in a generalized fashion, is probably not a generalized disorder of connective tissue of the type under discussion.

This condition is inherited as an autosomal recessive trait,[177,179] usually appears very early in life, like osteogenesis imperfecta may be detected in utero, involves the entire skeleton, and may result in such encroachment of the petrified osseous structure on the hematopoietic space of the bone marrow that pancytopenia occurs as the main clinical feature.[155,158,164,179,181,183,186,187,193,194,195,210] Frequently, the disease pursues a less malignant course with, however, a tendency to fracture and to chronic osteomyelitis, especially of the jaw in association with dental infections. The bones are described by some as so hard as to turn the edge of a steel chisel and by others as more like chalk. Usually they are excessively brittle and susceptible to spontaneous fracture. Because of experience with many other progressive disease-syndromes of hereditary background, one is not surprised that mild adult cases occur.[158] Repeatedly, hereditary diseases which are at first considered to be only the province of the pediatrician, simply because doctors have learned to recognize only the childhood cases which are the most severe, are found in fact to occur in mild form which does not find clinical expression until later decades or is at least consistent with survival to adulthood. The original patient of Albers-Schönberg[151] was 26 years old and is said to have been living ten years later for re-examination by Reiche. Alexander's[152] patient was 43 years old. The nature of the basic defect is not clear.

Multiple enchondromatosis is another heritable and generalized disorder of a specialized variety of connective tissue, in this instance, cartilage. It is usually referred to as Ollier's disease.[162,178,196,198,204] It may be associated with angiomata in the soft tissue—Maffucci's syndrome.[153,159] In Maffucci's syndrome the angiomata may involve the gut.

Like the two conditions just mentioned—osteopetrosis and multiple enchondromatosis—hereditary exostoses,[173,175] which may be confused with enchondromatosis, probably cannot qualify for the group of generalized hereditary disorders of connective tissue because involvement is seemingly limited to a specialized variety of connective tissue. (Even in fibrodysplasia ossificans

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*Albers-Schönberg[151] was one man; this is not a syndrome named for two persons like the Ehlers-Danlos syndrome or the Grönblad-Strandberg syndrome. Care should be taken not to confuse osteopetrosis with osteopoikilosis, which was also first described in a definitive manner by Albers-Schönberg; some writers have evidenced this confusion.

progressiva this may be the case, fascia and aponeuroses being the specialized connective tissue involved.)

Von Recklinghausen's *neurofibromatosis* is inherited as an autosomal dominant. The histogenesis of the nerve-sheath tumors of this disorder is in dispute.[211] If the basic defect resides in the fibroblasts which produce the perineural and endoneural collagen fibers, then this condition might be considered a generalized variety of connective tissue. On the other hand, there is evidence[189] that the parent cell of the von Recklinghausen neurofibroma may be the Schwann cell which is generally considered a special derivative of the neural crest and not a mesenchymal derivative. The facts that abundant collagen is sometimes present in these tumors and that cells presumed to be of the Schwann cell lineage produce collagen fibers in tissue culture[190] presents perplexing problems of general biological nature as well as problems in the origin of these tumors. It may be that whatever the histogenesis of the nerve-sheath tumors, the pigmentary anomalies of the syndrome, the local exaggerations of growth, ("elephantiasis nervosum", etc.), the pheochromocytomas in relatively high incidence, scoliosis, and so on, can be considered as secondary or tertiary features resulting from the involvement of nerves.

Achondroplasia and *cleidocranial dysostosis*[171] are conditions limited to bone, but relatively generalized there. LeGros Clark[161] makes the interesting observation that, whereas there are certain similarities between the two disorders, achondroplasia involves "cartilaginous bones," whereas in cleidocranial dysostosis "membrane bones" are affected.

Clearly there are genetic differences in the tendency to *keloid* formation. Negroes and some Caucasian families are notoriously susceptible.

In *urticaria pigmentosa*, the specific pathologic lesion appears to be the accumulation of large numbers of mast cells in the corium and more rarely at other sites such as bone and lung.[162,166] Irritation of the skin lesions results in wheal formation, presumably from the release of histamine from the mast cells. The disease occurs most often in young individuals and usually pursues a self-limited course, disappearing completely at puberty in many cases.

Although the mast cell may legitimately be considered an element of connective tissue, there is very little to indicate that urticaria pigmentosa is hereditary. Cockayne[163] found reports of its occurrence once in two brothers, twice in two sisters, once in three sisters, once in the mother and cousin of an affected child, and once in male uniovular twins. However, the majority of writers have not been impressed by a familial aggregation of cases. In general the clinical behavior of urticaria pigmentosa is not that of a condition in which heredity is the major etiologic factor.

There are, on the other hand, hereditary syndromes which are too wide in their clinical expression, i.e., display abnormalities of other structures than connective tissues. Such a syndrome is that which goes by Werner's name.[172,197,203,206] The victim of the *Werner syndrome*, which is inherited as an autosomal recessive, displays short stature; slender limbs with stocky trunk; scleroderma-like changes, especially in the skin of the extremities, with the development of ulcers over the ankle malleoli, Achilles tendon, heels, and toes, with atrophy of the corium

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demonstrable microscopically; and with localized soft tissue calcifications; and finally premature arteriosclerosis with Mönckeberg calcification. However, the patients also display premature canites and balding, juvenile cataract,* weak high-pitched voice, atrophy of the epidermis as well as the corium, hypogonadism, osteoporosis, increased incidence of diabetes mellitus. This is an intriguing disorder as far as definition of the basic defect is concerned. One is reminded of myotonia dystrophica, in which baldness, cataract, and hypogonadism cannot in the present state of ignorance be related to the disorder of muscle.

Epithelial, as well as connective tissue, elements are also involved in the *Ellis–van Creveld syndrome*[157] and in the several varieties of hereditary osteo- and arthrodysplasias which have been reported[176,200,207,210] in association with dystrophy of the fingernails.

In 1928 Pelger and in 1931 Huët, both of the Netherlands, described an anomaly of the nucleus of the leukocyte which in essence consists of a deficiency in segmentation.[208] It was found to be inherited as a dominant. Nachtscheim[191] found the anomaly in one person in 1,000 in the population of Berlin. What ostensibly is the same anomaly occurs in the rabbit where again it is inherited as a dominant. When two animals affected with the nuclear anomaly are bred, it is found that those offspring which are presumably homozygous for the Pelger-Huët trait demonstrate a severe form of chondrodystrophy.[180,191] The trait is lethal or sublethal in this homozygous form. At least one instance in man of a presumed homozygous form of *Pelger-Huët anomaly* has been reported.[170] Although the change in the leukocyte was more striking than usually seen, no skeletal abnormality was detected. The basis of the relationship between the nuclear anomaly and the chondrodystrophy in the homozygous rabbits is obscure.

In *Dupuytren's contracture*[156,201,205] and in *Peyronie's disease*[199] there is convincing evidence of an hereditary basis. However, the changes are confined to the connective tissue of the palmar fascia and of the corpus cavernosum, respectively.

There are a large number of members of the epiphysitis or *aseptic necrosis* group of disorders, in which, more perhaps than in any other area of medicine, eponyms abound and confound. The following fine entities are only a partial enumeration:

Tubercle of tibia	Osgood-Schlatter.
Head of femur	Legg-Calvé-Perthes.
Spine	Scheuermann.
Tarsal scaphoid	Köhler.
Semilunar	Kienböck, etc.

All of these probably have an hereditary background although the evidence in Legg-Perthes' disease is most complete. It is peculiar that each seems to be a distinct genotypic entity. There is, for example, no evidence that more

*The internist must keep the Werner syndrome[188] in mind in connection with patients who appear to have a more conventional, acquired variety of scleroderma. Cataracts can be the tip-off to the presence of this hereditary syndrome.

than one of these entities occurs in the same patient or that one member of an affected family has one variety whereas another member has a different variety. Interestingly, Legg-Perthes' disease probably almost never occurs in bona fide form in the pure Negro although a simulating condition occurs with sickle cell-hemoglobin C disease.[202]

In the case of *epidermolysis bullosa hereditaria* there is a view[167,174,209] of long standing that the basic defect is a deficiency of the elastic fibers of the superficial (papillary) layer of the corium. Normally these fibers are thought by some to bind the epidermis to the corium and their absence has been thought to explain adequately the bullous lesions of this congenital disorder. Others[165,182] have questioned this theory mainly on the basis of a failure to confirm the deficiency of elastic fibers on which the theory was predicated. The mucous membranes of the mouth have been involved but no specific internal lesions have been described in autopsied cases.[165,182]

For a discussion of the Morquio-Brailsford syndrome and of arthrogryposis multiplex congenita, see the section on the Hurler syndrome.

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G. The Future in the Study of Heritable Disorders of Connective Tissue

Undoubtedly, some of the most important problems in connection with these heritable disorders concern pathogenetic (phenogenetic) mechanisms. In the case of each entity here discussed, what information is available has been surveyed. However, our knowledge of the basic defects involved and the links in the pathogenetic chain leading to each of the multiple manifestations is pitifully limited. Snyder[233] expresses well the present direction of interest in genetics:

> In the early days of the study of genetics, the geneticist was content to establish the correlation between the gene in the chromosome and the characteristic in the individual, without raising much question as to the chain of events which connected the two. The attitude was very much like that of the traveler who boards the Miami train in New York confident that he will step out at the Miami station, but actually knowing very little about the physico-chemical principles of the Diesel engine or the intricacies of the switching and signaling systems that will get him there.
>
> Today, however, the question of genic action in the development of finished characters is uppermost in the minds of geneticists, and biochemical genetics is leading the attack on this front.

Physiologic genetics is the term customarily used for that division of the field concerned with tracing the link between gene and phene. The term is not precisely applicable to the study of mechanisms in disease traits. To be sure, it is often difficult to draw the line between pathologic states and deviations from the physiologic average. However, the term *genetic pathology* is probably a better one for the discipline concerned with the same problems in connection with heritable disease which the physiologic geneticist deals with in the case of traits such as skin color or polydactylism.

Many different technologic approaches to identification of the fundamental biochemical defect in these conditions must be adopted. Electron microscopy

has already been applied to the Ehlers-Danlos syndrome,[234] to pseudoxanthoma elasticum,[234] and to osteogenesis imperfecta.[218] Tissue culture of fibroblasts is possibly one of the more promising, although as yet unexplored, techniques for the study of heritable disorders of connective tissue. (In general, tissue culture has been too little used in physiologic genetics.) In vitro fibrogenesis has been investigated with the assistance of light microscopy[214,217,227,229,230] and electron microscopy,[20] but not in these diseases. Synthesis of certain of the constituents of the ground substance has also been studied in tissue culture.[224,229] Methods for chemical quantification of collagen production in vitro are available.[223] Tissue culture, or rather organ culture, has been employed in some hereditary developmental anomalies of animals[216,219,220,221] but except for the studies of Geiger and Garvin[222] on muscle from patients with muscular dystrophy, tissue culture methods have not, to my knowledge, been utilized in the study of hereditary disorders of man.

In connection with the heritable disorders of connective tissue, the first objective of tissue culture studies should be the in vitro replication of the morphologic abnormalities. In osteogenesis imperfecta and in the Hurler syndrome one can with justification anticipate success in demonstrating morphologic abnormality, in the fibers formed in the first instance, possibly in the fibroblast itself in the second, i.e., the "gargoyle cell" may be demonstrable in culture. It is possible that the fibers produced by fibroblasts from patients with pseudoxanthoma elasticum might be morphologically abnormal or undergo premature deterioration. In the Marfan syndrome and the Ehler-Danlos syndrome, morphologic abnormality is much less likely to be evident. However, if in the latter condition there is failure to observe excessive production of elastic fibers, then significant negative evidence bearing on the nature of the basic defect will have been provided. Much interest is attached to observations of cultures of fascial fibroblasts from patients with fibrodysplasia ossificans progressiva.

If the initial morphologic studies are consonant with the view that a fibroblast strain growing in the test tube represents the original donor's disease "in pure culture," then intensive studies should be undertaken of the chemical character of the fibers and ground materials produced by the cells, e.g., amino acid profile of the collagen and elastin. Rate of fibrogenesis must be quantified.

Generalized disorders of connective tissue which satisfy the criteria of these studies seem to be almost completely unknown in animals.[228] Their existence in animals is likely, however. More easily recognized disorders, such as achondroplasia, do occur in many species and the Pelger-Huët anomaly of leukocytes with associated chrondrodystrophy occurs in the rabbit. As noted in the appropriate sections, conditions in animals resembling OI and FOP in man have been described. The whole body of knowledge about connective tissue and perhaps understanding of the hereditary disorders of connective tissue in man could be greatly advanced if there were available animal strains containing a mutant gene determining an aberration of connective tissue.

Not only do diverse disciplines have much to offer in the elucidation of pathogenetic mechanisms in these disorders of connective tissue, but also, conversely, these heritable disorders per se can be exploited as valuable tools for the investigation of connective tissue in general.

Through the attention of the rheumatologist, the advent of steroid therapy, the increased familiarity with systemic lupus erythematosus and related so-called "collagen diseases"[226] or "connective tissue diseases,"[225] connective tissue has in recent years come into its own as an object of medical interest. As objects of study the heritable disorders of connective tissue have conspicuous advantages over these acquired conditions. The lesion tends to be more selective, i.e., can better be pin-pointed to one element of connective tissue. The biochemical lesion is, one would presume, definable in a more clean-cut manner. These hereditary disorders of connective tissue are in themselves of sufficient clinical importance to justify intensive study of basic pathogenesis. But, in addition, they can be looked upon as tools by use of which much has been, and much more can be, learned about the biology of normal connective tissue and the reactions of connective tissue in acquired disease.

Great interest was stimulated by the discovery by Ponseti and Baird[231] that seed of the sweet pea (*Lathyrus odoratus*) contains a substance (subsequently identified as an aminonitrile) which is a specific toxin for some connective tissue element. This announcement created a stir, in part because of a similarity of the lesions observed in rats to those encountered under some circumstances in man, but more because there seemed here to be a tool for indirectly getting at normal mechanisms in connective tissue. Vitamin C deprivation[235,236] has likewise been and promises to continue to be a useful tool for studying such matters as collagen fibrogenesis and the relation of the ground substance to same. As unitary defects of connective tissue elements, the heritable disorders of connective tissue also represent potentially productive areas for investigation.

I do not intend to create the impression that there is no longer opportunity for studies of this group of disorders on the clinical level.[213] This is by no means the case. The genetics of all of these conditions requires further investigation. Improved means for recognizing mild forms of the several disorders would have some practical usefulness and would increase understanding of the mechanisms of inheritance. Similarly, clinical analyses of the factors responsible for variability in expression of these syndromes could have both practical and theoretical implications of importance. For the benefit of the patients, methods for modifying the clinical expression of the disorders should be sought.

In the case of several of the syndromes, particularly pseudoxanthoma elasticum and the Ehlers-Danlos syndrome, information on internal medical ramifications is still regrettably scanty. Knowledge in this area depends on the continuation of clinical and pathologic observations of the classical type.

In general, the future of study of heritable disorders of connective tissue looks exciting and promises productivity which will have significance far outreaching that relating to the clinical problems presented by these patients.

GENERAL SUMMARY AND CONCLUSIONS

1. In general, the clinical picture of each of the heritable disorders of connective tissue is as specific and predictable as that of other clinical entities, for example, infectious diseases. There is, of course, a certain amount of variability in clinical expression, such as the physician learns to expect. The clinical

manifestations of each syndrome were summarized in tabular form in Section I of this series.

2. The heritable disorders of connective tissue are not congenital malformations in the conventional sense. Certain congenital malformations do seem to occur with increased frequency in association with some of these disorders. It is proposed that during embryogenesis the connective tissue defect sets the stage favorable to the development of the particular malformations. See the section on the Marfan syndrome for examples.

3. Pseudoxanthoma elasticum behaves like an abiotrophy as does also the aortic involvement in the Marfan syndrome. The peculiarities of growth in the Marfan syndrome and the Hurler syndrome are apparently intimately related to the basic defect of connective tissue. Certain features of the Hurler syndrome (specifically those relating to the brain, liver, spleen, and cardiovascular system) partake of the characteristics of a thesaurosis, or "storage" disease. In osteogenesis imperfecta and in the Ehlers-Danlos syndrome there appears to be a defect in the formation of collagen; in the first the defect is relatively early in fibrogenesis, whereas in the second the organization of collagen bundles into the usual meshwork is defective.

4. Many principles of heredity are illustrated by these disorders. Examples of dominant, recessive, and sex-linked inheritance are provided. Phenomena of expressivity and penetrance are displayed.

5. The recognition of the more easily detectable expressions of the basic defect of connective tissue provides clinical clues to the nature of internal disturbances which are less accessible for study. Most dramatic illustrations of this time-honored principle are the association of ectopia lentis with aortic regurgitation in the Marfan syndrome and of angioid streaks of the fundus oculi and characteristic skin changes with massive gastrointestinal hemorrhage in pseudoxanthoma elasticum.

6. The heritable disorders of connective tissue can be useful tools for the study of the normal biology of connective tissue. Further confirmation is provided for the principle enunciated by Sir Archibald Garrod: The clinical and other investigation of hereditary disorders will shed light on normal developmental and biochemical mechanisms.

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Editorials

THE USE OF PREDNISONE IN RHEUMATIC DISEASES

The exciting history and rapid development of our knowledge of the chemistry, physiology, and clinical use of the adrenocortical steroids and corticotropin are too well known to require repetition here. For general orientation, the history, during the past quarter of a century, of the biochemical and organic chemical aspects of these hormones may be conveniently divided into three stages:

a. The preparation of biologically active *extracts* (1930—Swingle and Pfiffner, Hartmann and his associates).

b. The *isolation* of crystalline steroid hormones from the adrenal cortex (1934—Kendall, Pfiffner, Reichstein and Wintersteiner), biologically pure corticotropin from the adenohypophysis (1943—Li and Sayers), and aldosterone from amorphous fraction of adrenal cortex (1954—Reichstein, Simpson and associates).

c. The *synthesis* of biologically active 21 carbon steroids: desoxicorticosterone (1937-Steiger and Reichstein), cortisone (1946-Kendall and Sarett), the halogenated steroids (1954-Borman and Fried and their respective collaborators) and the "delta-1" steroids (1954-Herzog and associates).

The observation of the striking clinical effects of cortisone, hydrocortisone, and corticotropin in the rheumatic diseases was first reported by Hench and his associates in 1949.[1] From these studies it became apparent that of some 30 steroids isolated from the adrenal cortex only the 11, 17 oxygenated steroids (cortisone and hydrocortisone) possessed anti-inflammatory properties. Since these were found, in some cases, to produce serious side effects and in others to lose their effectiveness upon protracted administration, it was natural to explore the potentialities of the synthetic 11, 17 oxygenated steroids as soon as they became available.

Initial reports on the clinical trials of the synthetic halogenated steroids (9 alpha-fluorohydrocortisone) in rheumatoid arthritis were made in 1954 simultaneously by Boland, Bayles, and Bunim,[2] of the synthetic "delta-1" steroids (prednisone and prednisolone) in the same disease by Bunim and his associates[3] in 1954, and, finally, of the unsaturated, halogenated steroid (delta 1, 9 alpha-fluorohydrocortisone) in rheumatoid arthritis by the latter author and his collaborators[4] in 1955.

Prednisone and prednisolone were introduced into clinical medicine one year ago. The original generic terms were metacortandracin and metacortandralone. These steroids, the analogues of cortisone and hydrocortisone, respectively, were synthesized by Herzog and his collaborators.[5] The synthetic steroids differ

from their parent compounds by the presence of a double bond between carbons 1 and 2 in the A ring. Milligram for milligram, they are about three to four times more potent than the parent steroids as measured by their capacity to effect glycogen deposition in the liver of an adrenalectomized rat.[6] It is noteworthy that the enhanced glucocorticoid activity of prednisone and prednisolone observed in the experimental animal matches the increased anti-inflammatory and antirheumatic activity found in patients with rheumatoid arthritis,[3] systemic lupus erythematosus,[7] scleroderma,[8] and rheumatic fever.[9,10] Like cortisone and hydrocortisone, the unsaturated oxysteroids inhibit the release of corticotropin by the adenohypophysis, thus suppressing adrenocortical activity. The effect of the new steroids on protein, carbohydrate, fat, and calcium metabolism is qualitatively the same as that of cortisone. Upon administration of prednisone, nitrogen excretion is increased, carbohydrate tolerance is reduced (insulin requirement in diabetic patients is increased), excessive fat deposits occur, and a negative calcium balance may result. The principal attribute of prednisone and prednisolone is that, unlike cortisone, hydrocortisone, or the halogenated steroids, they do not cause retention of sodium or increased excretion of potassium when administered in usual therapeutic doses (less than 50 mg. daily).

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Patients with rheumatoid arthritis who have had diminishing benefits from prolonged administration of cortisone and whose response to the hormone had become decidedly unsatisfactory, often exhibit marked initial improvement when given prednisone. In some cases, the improvement again lessens after months of prednisone therapy, but in many patients observed for one year, the favorable effects are sustained. The mechanism for these phenomena is not clear.

Unfortunately, the serious side effects that have been encountered in long-term cortisone therapy have also developed with prednisone administration.[11] Ulcers of the stomach or duodenum have appeared during the early weeks or months of prednisone therapy in patients who were known to have no lesions prior to treatment. Severe hemorrhage and sudden perforation have also occurred. These catastrophes are usually unheralded and no opportunity is given the physician either to reduce dosage or to discontinue the drug in time to avoid trouble. Asymptomatic peptic ulcers, detected by routine, periodic radiographic examination, healed despite continued prednisone therapy when antacids and anti-ulcer regimens were instituted.

Other serious side effects, less common than gastrointestinal lesions, are mental and emotional disturbances (psychosis in some cases) and pathologic fracture of vertebral bodies, ribs, or, infrequently, long bones. Among the less serious, unwanted effects are facial rounding, abnormal fat deposits, cutaneous purpuric manifestations, leg cramps, weakness, fatigue, recurrence of menopausal sweats and flushes, hirsutism, acne, and, rarely, hypertension.

It is obvious that administration of prednisone or prednisolone calls for close medical supervision and unending vigilance. The smallest possible dose consistent with reasonable comfort is desirable. Patients should be carefully selected and steroid therapy instituted only when it is clear that expected results

warrant the risks involved. The contraindications to prednisone therapy are essentially the same as obtain for cortisone therapy with the notable exception of edema or congestive heart failure resulting from sodium and water retention. It should be emphasized that prednisone alone, like cortisone alone, certainly does not constitute complete treatment. There is no substitute for a comprehensive, individualized program of care for the patient with a rheumatic disease.

The search continues for a drug to combat these mesenchymal diseases which is more satisfactory than cortisone, hydrocortisone, prednisone, or prednisolone. Resourceful organic chemists are at work synthesizing new compounds with almost every conceivable alteration in the structure of the steroid nucleus, with the goal of lessening or overcoming the undesirable effects yet retaining the potent anti-inflammatory properties of the steroids that have already been tested. Upon their achievement rest the hopes of the clinician for an effective and nontoxic antirheumatic agent.

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RELATION OF NUTRITION TO ETIOLOGY AND TREATMENT OF LAENNEC'S CIRRHOSIS

In the past twenty years there has been considerable progress in understanding the nature of Laennec's cirrhosis.[1] The suggestion that malnutrition plays an important etiologic role has been based upon three observations, namely the prevalence of Laennec's cirrhosis in areas where nutritional deficiency disease is endemic; the frequent association of cirrhosis with alcoholism; and the favorable effect of a nutritious diet upon the course of the disease.[2] Although diffuse portal cirrhosis may develop on occasion as the result of poisoning by carbon tetrachloride and possibly from viral hepatitis, the majority of cases appear to be related to malnutrition. When Laennec's cirrhosis is encountered in association with alcoholism, diabetes mellitus, dysentery, parasitic infestations, or malaria, these diseases appear to serve as secondary or conditioning factors. Kwashiorkor, a polydeficiency disease in which fatty cirrhosis of the liver is seen, probably belongs to the same class of hepatic disorder as Laennec's cirrhosis.

Further evidence of the close relation between malnutrition and hepatic cirrhosis has been derived from a series of impressive experimental studies.[3-6] The disease has been reproduced in the rat by means of low protein diets which are specifically deficient in choline or methionine. Although the assumption was not made that Laennec's cirrhosis and experimental nutritional cirrhosis are identical disease processes, their resemblance is striking. However, there remain several unanswered questions. In what way does choline or methionine deficiency bring about hepatic cirrhosis? Does the lack of an essential substance cause disintegration of the liver cell, or does it render the cell susceptible to unidentified endogeneous toxins? What are the steps involved in the pathogenesis of the disease? Do the inflammatory cellular reaction and the fibrosis result from rupture of the cell by fatty cysts, as suggested by Hartroft,[7] or is there in addition some biochemical lesion which leads to the death of the liver cell and overgrowth of connective tissue? What are the factors that predispose the male more than the female to hepatic cirrhosis, both in the experimental animal and in the human subject?

Some believe that Laennec's cirrhosis pursues a progressive course uninfluenced by therapy, but most workers agree that the disease can be arrested by means of a highly nutritious diet, bed rest, and supportive measures. Disagreement as to prognosis has been due in part to the varied nomenclature employed in different countries. A sharp delineation between Laennec's cirrhosis and postnecrotic cirrhosis is made by some workers and not by others. It is my conviction that the two diseases are distinct and that Laennec's cirrhosis is benefited far more by dietary therapy than is postnecrotic cirrhosis.

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Well-controlled studies to evaluate the response to dietary therapy in Laennec's cirrhosis are not at hand because of practical difficulties. Characteristically, the patient enters the hospital only when he is very ill. He is put to bed. Alcohol is interdicted. If there has been hemorrhage he is transfused. If there is intercurrent infection he receives antibiotics. Other supportive agents are provided as needed. If one were to design a suitably controlled study the alcoholic patient should be kept inebriated and fed a basal diet of negligible nutrient value to which would be added one food factor at a time. A specifically potent factor might be discovered in this fashion, but this seems unlikely because the signs of recovery that are seen today are too gradual to suggest a single, potent therapeutic agent. In short-term studies, patients have shown recovery from jaundice after being placed at bed rest and on a low protein basal diet without alcohol. Progressive improvement, however, does not occur unless a nutritious diet, including adequate protein is provided.[8] With inadequate intake of protein, regenerative changes in the liver can take place only at the expense of tissue protein elsewhere. The need for specific adjuvants, such as choline or methionine, has not been established in the treatment of Laennec's cirrhosis. Contradictory opinions have been expressed by various workers concerning their efficacy. It seems plausible that if a nutritious diet supplies optimal amounts of these factors, an excess will be of little benefit.[9]

A number of studies have tested the value of certain dietary factors in the treatment of nutritional cirrhosis in the rat. In general, these indicate that choline, and particularly methionine, when added to a basal, low protein diet, help to prevent further liver damage. However, optimal repair and regeneration takes place only when a nutritious diet, rich in protein or balanced amino acids, is fed.[10,11] The extent of recovery likewise depends upon the stage of the disease at which therapy is begun. These findings seem to be in agreement with clinical experience. Adequate dietary intake of protein appears to be basic to the effective treatment of this disease.

Recent observations, however, have indicated that in the presence of overt or threatened hepatic coma, the intake of protein should be sharply reduced.[12] This would seem to be a paradox in view of the previous endorsement of high protein feeding. Inquiry into the nature of hepatic coma (cholemia) has been one of the most interesting developments in the field of hepatic investigation. It may be recalled that for many years a low protein, high carbohydrate diet was advocated in this country and abroad. This regimen was based in part on the finding that dogs with Eck fistula became comatose when fed a meat diet. Later studies by Van Caulaert[13] and by Kirk[14] demonstrated that the cerebral disturbance in hepatic failure may be related to intoxication with ammonia. Scant notice was taken of these studies until recent years, when the clinical importance of elevated blood ammonia in relation to hepatic coma was rediscovered. Phillips and his co-workers[12] have shown that cholemia could be induced by feeding ammonium salts or high protein diets to patients with cirrhosis of the liver. who were on the verge of hepatic failure. Similar studies have been carried out by Stahl[15] and by White[16] and their associates. These authors point out that the correlation between values for blood ammonia and the presence of coma is good

but not invariable. They suggest that ammonia itself may not be the toxic factor, but that it may indicate the presence of an associated toxic factor.

The practical application of these studies has been of great value. In the presence of impending cholemia, as evidenced by drowsiness, confusion, or flapping tremors, it is advisable to reduce the intake of protein to 75 Gm. or even to 50 Gm. daily until these symptoms subside. Intravenous infusions of glucose and the administration of antibiotics (to decrease the bacterial content of the intestine) are helpful adjuvants.

It may be emphasized that most patients with Laennec's cirrhosis tolerate diets containing 100 to 150 Gm. of protein very well, and indeed thrive on such regimens.[2] If we are alert to the limitations imposed by cholemia, it still appears reasonable for the patient to ingest as much protein as he can tolerate efficiently, and by this means to further the reparative process.

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*The bibliography, of necessity, is limited to only a few of the many articles dealing with the subject matter of the editorial.

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DE QUERVAIN'S DISEASE

Pain at the wrist near the base of the thumb about ½ inch proximal to the radial styloid is sometimes attributed to injury or chronic trauma but its exact diagnosis is often missed. Such pain and exactly localized tenderness is usually due to de Quervain's disease.[5] This disease is *stenosing tendovaginitis at the radial styloid process of the wrist* and involves the abductor longus and extensor brevis tendons of the thumb. A description of the disease is to be found in the thirteenth edition of *Gray's Anatomy* published in 1893 under the name of "washer woman's sprain." De Quervain described definitive treatment for the disease in 1895.

In order to evaluate the position of this disease in the general group of pathologic conditions affecting the relations between tendons and the sheaths in which they glide, one must consider the difference between *stenosing tendovaginitis* and *tenosynovitis*.

Tenosynovitis, which has also been called tendovaginitis crepitans,[2] is primarily an inflammation of the cellular mucin-producing lining membrane of the fibrous tissue tube, or vagina, in which a tendon glides back and forth. It is identified clinically by palpable crepitus or "wash-leather creaking"[8] over the tendon as it is moved. The area of "creaking" is often widespread over the length of the sheath of the tendon and is tender. Tenosynovitis can be painful and disabling. It often follows a short period of unusual activity of a certain muscle tendon unit; for instance, tenosynovitis of the long and short radial extensors of the wrist may develop during unaccustomed spading of a garden. Abnormal pressure on a tendon and its sheath may cause tenosynovitis, as, for instance, when the counter of a new shoe presses on the Achilles tendon. A sharp blow to a heel cord can also cause synovitis of the sheath of the Achilles tendon. Infections, or a foreign body such as the tip of a thorn, or connective tissue diseases such as gout or rheumatoid arthritis may cause tenosynovitis.

In those instances in which the etiological agent is trauma, immobilization of the involved muscle tendon unit and injection of hydrocortisone acetate into the space between the tendon and the synovial lining of the tendon sheath will usually effect a cure in one to three weeks.

Stenosing tendovaginitis is a quite different disease. It primarily involves the fibrous wall at special parts of the tendon sheath, rather than simply the lining synovium of the whole sheath. This disease occurs where a tendon passes through a fibrous ring or pulley. These pulley or ring regions of the tendon sheath usually lie over bony prominences. Part of the ring is often a groove in the bony prominence, the ring being completed by a specialized thickened portion of the tendon sheath. The initial pathologic lesion is an abnormal proliferation of the fibrous tissue in this ring so that the space, normally present in the center of the ring through which the tendon glides, is encroached upon.

Secondarily, the tendon becomes constricted at this pulley region by the hypertrophied fibrous ring, while just distal and to a less degree proximal to the point of constriction the tendon becomes bulbously enlarged.

These changes set the stage for a dramatic clinical syndrome which may be disabling but not always painful. The bulbous expansion of the tendon may be just small enough to permit its passage through the thickened ring or pulley region of its sheath. It can be pulled through by its own muscle but often it cannot be returned through the constricting pulley by the antagonist muscles. Thus the clinical syndrome of locking or snapping finger and toe is developed. The patient can flex the involved finger or toe but must make great effort or use the fingers of the opposite hand to extend the digit again. Finally, as extension is forced, the bulbous portion of the tendon pops back through the thickened and constricted and fixed portion of the tendon sheath and the finger "snaps" or "unlocks" into the extended position.

The most common sites for such thickened tendon sheath rings or tunnels are on the palmer aspects of the heads of the metacarpals, the plantar aspect of the heads of the metatarsals, and on the dorsoradial aspect of the distal end of the radius about ½ inch proximal to the tip of the radial styloid.

Finkelstein[2] experimentally produced stenosing tendovaginitis in animals by chemical, mechanical, and thermal trauma.

Multiple strands in involved tendons at the radial styloid area of the wrist emphasized by Bunnell[1] might suggest that some abnormality might exist in the original development of those tendon-tendon sheath units, that eventually develop stenosing tendovaginitis. However, Loomis,[4] and Lacey, Goldstein, and Tobin[3] noted that the incidence of aberrant tendons at surgical operation approximated the incidence in unselected cadaver material.

The clinical observations presented by Watson-Jones,[7] in respect to multiple incidence of bulbous enlargement of the long flexor tendons of the fingers and toes in any one patient, suggest that a nonpainful constriction of the tendon sheath around the tendon, at least in the case of finger and toe flexor tendons, may predispose to the development of the painful disability known as stenosing tendovaginitis.

When the complication of synovitis secondary to stress, over a long or short time, develops in these previously abnormal but often asymptomatic "pulley" regions of a tendon-tendon sheath system, acute painful limitation of motion may suddenly occur. One usually finds the involved finger or toe locked in flexion. Efforts to extend the digit aggravate the pain. Point tenderness exists over the fibrous pulley ring of the involved tendon sheath.

In the case of the short extensor and long abductor of the thumb, "locking" is not so obvious although the patient usually shows voluntary inability to flex or extend and abduct the involved thumb. Passive motion in both directions is limited or nonexistent. If the thumb is partly flexed into the palm of the hand and the patient then closes his fingers over the thumb, while the examiner strains the wrist into ulnar deviation, excruciating pain is felt in the region of the radial styloid. This test may duplicate part of the patient's complaint, for the pain thus produced may radiate up and down the radial aspect of the forearm and hand. Careful localizing palpation over the radial styloid region reveals a deep small area of tissue swelling, in the center of which one can usually palpate a small thickened area that moves a little under the skin as the thumb is flexed

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and extended. Acute point tenderness is found in this area. No grating is usually felt on the slight movement of the tendons. X-rays of this area are usually negative.[6]

This particular type of stenosing tendovaginitis occurring over the radial styloid process of the wrist is known as *de Quervain's disease.* Unless properly diagnosed, much effort is wasted on useless treatment. Immobilization and hydrocortisone locally have been found effective in relieving the acute symptoms in a very few patients. After such treatment the stenosis of the tendon sheath persists and symptoms usually recur, particularly if the precipitating factor was some habitual motion of the hand associated with the patients occupation. However, stenosing tendovaginitis at the radial styloid does respond dramatically to a simple surgical procedure in which the constricting and thickened tendon sheath is longitudinally incised and partially excised. This effective surgical procedure was described in 1895 by de Quervain[5] for definitive treatment of this particular form of chronic tendovaginitis at the radial styloid of the wrist. This basic procedure can be used for treatment of chronic tendovaginitis in other sites. To be effective the surgeon must be sure to find and free any involved but aberrant tendons that have separate sheaths in the radial styloid area.[4]

The effectiveness originally claimed for this procedure has stood the test of time and its wide and successful application by many orthopedic surgeons attests to its soundness.

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Book Review

KLINIK UND THERAPIE DER VERGIFTUNGEN. By Sven Moeschlin. Pp. 521. Indexed. Stuttgart, Germany, 1955. George Thieme Verlag. (In the U. S. A. and Canada, The Intercontinental Medical Book Corporation, New York, N. Y.). Price $14.05.

This book by an eminent European physician is now in its second edition. It has been translated into several foreign languages, but has not yet appeared in an English edition. The field of toxicology is inherently difficult to describe in a fashion which is complete, authoritative, *or* readable, let alone all three. Dr. Moeschlin has made a good try at achieving a definitive text, and his book is at least as good as many on this subject available in English. It has defects, such as occasional questionable therapeutic advice or failure to refer to key articles in literature, but so has every other text on toxicology. The barrier posed by the publication of the work in German is sufficient to minimize the usefulness of this book for the American public. The publishers would be well advised to consider an English edition if they desire to compete successfully with already available texts on this subject.

Louis Lasagna

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